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(54) Title: **EXPRESSION PROFILES FOR COLON CANCER AND METHODS OF USE**

(57) Abstract: The present invention relates to gene expression profiles for colon cancer, microarrays comprising nucleic acid sequences representing gene expression profiles, and methods of using expression profiles and microarrays. The invention also provides methods and compositions for diagnostic assays for detecting cancer and therapeutic methods and compositions for treating cancer. The invention also provides methods for designing, identifying, and optimizing therapeutics for cancer.

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## EXPRESSION PROFILES FOR COLON CANCER AND METHODS OF USE

[001] This application claims benefit of U.S. Provisional Application Serial No. 60/442,582, filed January 24, 2003, the contents of which are incorporated herein by reference in their entirety.

### FIELD OF THE INVENTION

[002] The present invention relates to gene expression profiles for colon cancer, microarrays comprising nucleic acid sequences representing gene expression profiles, and methods of using expression profiles and microarrays.

### BACKGROUND OF THE INVENTION

[003] Many disease states are characterized by differences in the expression levels of various genes either through changes in the copy number of the genetic DNA or through changes in levels of transcription of particular genes (e.g., through control of initiation, provision of RNA precursors, RNA processing, etc.). For example, losses and gains of genetic material play an important role in malignant transformation and progression. These gains and losses are thought to be "driven" by at least two kinds of genes, oncogenes and tumor suppressor genes. Oncogenes are positive regulators of tumorigenesis, while tumor suppressor genes are negative regulators of tumorigenesis (Marshall, Cell 64:313-326, 1991; Weinberg, Science 254:1138-1146, 1991). Therefore, one mechanism of activating unregulated growth is to increase the number of genes coding for oncogene proteins or to increase the level of expression of these oncogenes (e.g., in response to cellular or environmental changes), and another mechanism is to lose genetic material or to decrease the level of expression of genes that code for tumor suppressors. This model is supported by the losses and gains of genetic material associated with glioma progression (Mikkelsen, et al., J. Cellular Biochem. 46:3-8, 1991). Thus, changes in the expression (transcription) levels of particular genes (e.g., oncogenes or tumor suppressors) serve as signposts for the presence and progression of various cancers.

[004] Compounds which are used as therapeutics to treat these various diseases (e.g., cancer) presumably reverse some, or all, of these gene expression changes. The expression change of at least some of these genes may therefore, be used as a method to monitor, or even predict, the efficacy of such therapeutics. The analysis of these expression changes may be performed in the target tissue of interest (e.g., tumor) or in some surrogate cell population (e.g., peripheral blood leukocytes). In the latter case, correlation of the gene expression changes with efficacy (e.g., tumor shrinkage or non-growth) must be especially strong for the expression change pattern to be used as a marker for efficacy.

[005] A number of laboratories have reported success in using gene expression analysis, via microarrays or other methods, to classify human tumors at the molecular level (Bittner, et al., Nature 406:536-540, 2000; Alon, et al., Proc. Natl. Acad. Sci. USA 96:6745-6750, 1999; Alizadeh, et al., Nature 403:503-511, 2000; Golub, et al., Science 286:531-537, 1999; Perou, et al., Proc. Natl. Acad. Sci. 96:9212-9217, 1999; Kahn, et al., Am. J. Pathol. 156:1887-1900, 2000). Genes, either individually or as a subset, identified in this way may be used as markers that could be tracked for changes that correlate with efficacy of a therapeutic compound(s) or to predict which patients might benefit from a particular therapeutic. Total RNA was isolated from ten human colon tumors and from normal adjacent tissue (NAT), and the RNA was analyzed from each sample using Affymetrix technology.

#### SUMMARY OF THE INVENTION

[006] The present invention relates to gene expression profiles for colon cancer, microarrays comprising nucleic acid sequences or amino acid sequences representing expression profiles, and methods of using expression profiles and microarrays.

[007] In one embodiment of the present invention, the gene expression profile is an expression profile comprising one or more genes (e.g., SEQ ID NOs: 1-96) that demonstrate altered expression in human colon tumors versus normal adjacent tissue (NAT).

[008] In another embodiment, the expression profile is an expression profile comprising one or more polypeptides (e.g., SEQ ID NOs: 97-191) that demonstrate altered expression in human colon tumors versus normal adjacent tissue (NAT).

[009] In further embodiment of the present invention, the gene expression profile may be an expression profile comprising one or more genes selected from the group consisting of the genes listed in the Table 1 to 3. In another embodiment of the present invention, the gene expression profiles comprise one or more biomarkers isolated from the group comprising the genes listed in the Tables.

[010] The present invention is also directed to the discovery of the gene expression profile of human colon tumors and normal adjacent tissue. As described in the Examples and in the Tables, human colon tumors have genes which are expressed at higher levels (i.e., which are up-regulated) and genes which are expressed at lower levels (i.e., which are down-regulated) relative to normal adjacent tissue. Sets of genes which are up-regulated or down-regulated are referred to herein as "genes characteristic of human colon tumor tissue."

[011] Also within the scope of the present invention are microarrays comprising one or more genes that demonstrate altered expression in human colon tumor tissue. In another embodiment of

the present invention, the microarray may be a microarray comprising one or more genes selected from the group consisting of the genes listed in the Tables. In a further embodiment, the microarray may be a microarray comprising one or more biomarkers isolated from the group comprising the genes listed in the Tables.

[012] In addition, it is an objective of the invention to provide methods and reagents for the prediction, diagnosis, prognosis, and therapy of cancer.

[013] This invention also relates to methods for using said microarrays which include, but are not limited to, screening the effects of a drug or treatment on tissue or cell samples, screening toxicity effects on tissue or cell samples, identifying a disease state in a tissue or cell sample, providing a patient diagnosis, predicting a patient's response to treatment, distinguishing between control and drug-treated samples, distinguishing between normal and tumor samples, discovering novel drugs, and determining the level of gene expression in a tissue or cell sample.

[014] Another embodiment of the present invention is a method for screening the effects of a drug on a tissue or cell sample comprising the step of analyzing the level of expression of one or more genes (e.g., SEQ ID NOs: 1-96) and/or gene products (e.g., SEQ ID NOs: 97-191), wherein the gene expression and/or gene product levels in the tissue or cell sample are analyzed before and after exposure to the drug, and a variation in the expression level of the gene and/or gene product is indicative of a drug effect or provides a patient diagnosis or predicts a patient's response to the treatment.

[015] Another aspect of the present invention is a method for discovering novel drugs comprising the step of analyzing the level of expression of one or more genes and/or gene products, wherein the gene expression and/or gene product levels of the cells are analyzed before and after exposure to the drug, and a variation in the expression level of the gene and/or gene product is indicative of drug efficacy.

[016] The invention further provides a method for identifying a compound useful for the treatment of cancer comprising administering to a subject with cancer a test compound, and measuring the activity of the polypeptide (e.g., the polypeptides encoded by SEQ ID NOs: 97-191), wherein a change in the activity of the polypeptide is indicative of the test compound being useful for the treatment of cancer.

[017] The invention, thus, provides methods which may be used to identify compounds which may act, for example, as regulators or modulators such as agonists and antagonists, partial agonists, inverse agonists, activators, co-activators, and inhibitors. Accordingly, the invention provides reagents and methods for regulating the expression of a polynucleotide or a polypeptide associated with cancer. Reagents that modulate the expression, stability, or amount of a



polynucleotide or the activity of the polypeptide may be a protein, a peptide, a peptidomimetic, a nucleic acid, a nucleic acid analogue (e.g., peptide nucleic acid, locked nucleic acid), or a small molecule.

[018] The present invention also provides a method for providing a patient diagnosis comprising the step of analyzing the level of expression of one or more genes and/or gene products, wherein the gene expression and/or gene product levels of normal and patient samples are analyzed, and a variation in the expression level of the gene and/or gene product in the patient sample is diagnostic of a disease. The patient samples include, but are not limited to, blood, amniotic fluid, plasma, semen, bone marrow, and tissue biopsy.

[019] The present invention still further provides a method of diagnosing cancer in a subject comprising measuring the activity of the polypeptide in a subject suspected of having cancer, wherein if there is a difference in the activity of the polypeptide, relative to the activity of the polypeptide in a subject not suspected of having cancer, then the subject is diagnosed has having cancer.

[020] In another embodiment, the invention provides a method for detecting cancer in a patient sample in which an antibody to a protein is used to react with proteins in the patient sample.

[021] Another aspect of the present invention is a method for distinguishing between normal and disease states comprising the step of analyzing the level of expression of one or more genes and/or gene products, wherein the gene expression and/or gene product levels of normal and disease tissues are analyzed, and a variation in the expression level of the gene and/or gene product is indicative of a disease state.

[022] In another embodiment, the invention pertains to a method of determining the phenotype of cells comprising detecting the differential expression, relative to normal cells, of at least one gene, wherein the gene is differentially expressed by at least a factor of two, at least a factor of five, at least a factor of twenty, or at least a factor of fifty.

[023] In yet another embodiment, the invention pertains to a method of determining the phenotype of cells, comprising detecting the differential expression, relative to normal cells, of at least one polypeptide, wherein the protein is differentially expressed by at least a factor of two, at least a factor of five, at least a factor of twenty, an up to at least a factor of fifty.

[024] In another embodiment, the invention pertains to a method for determining the phenotype of cells from a patient by providing a nucleic acid probe comprising a nucleotide sequence having at least about 10, at least about 15, at least about 25, or at least about 40 consecutive nucleotides, obtaining a sample of cells from a patient, optionally providing a second sample of cells substantially all of which are non-cancerous, contacting the nucleic acid probe under stringent

conditions with mRNA of each of said first and second cell samples, and comparing (a) the amount of hybridization of the probe with mRNA of the first cell sample, with (b) the amount of hybridization of the probe with mRNA of the second cell sample, wherein a difference of at least a factor of two, at least a factor of five, at least a factor of twenty, or at least a factor of fifty in the amount of hybridization with the mRNA of the first cell sample as compared to the amount of hybridization with the mRNA of the second cell sample is indicative of the phenotype of cells in the first cell sample.

[025] In another embodiment, the invention provides a test kit for identifying the presence of cancerous cells or tissues, comprising a probe/primer, for measuring a level of a nucleic acid in a sample of cells isolated from a patient. In certain embodiments, the kit may further include instructions for using the kit, solutions for suspending or fixing the cells, detectable tags or labels, solutions for rendering a nucleic acid susceptible to hybridization, solutions for lysing cells, or solutions for the purification of nucleic acids.

[026] In one embodiment, the invention provides a test kit for identifying the presence of cancer cells or tissues, comprising an antibody specific for a protein. In certain embodiments, the kit further includes instructions for using the kit. In certain embodiments, the kit may further include solutions for suspending or fixing the cells, detectable tags or labels, solutions for rendering a polypeptide susceptible to the binding of an antibody, solutions for lysing cells, or solutions for the purification of polypeptides.

[027] In another embodiment, the invention provides a test kit for monitoring the efficacy of a compound or therapeutic in cancerous cells or tissues, comprising a probe/primer, for measuring a level of a nucleic acid in a sample of cells isolated from a patient. In certain embodiments, the kit may further include instructions for using the kit, solutions for suspending or fixing the cells, detectable tags or labels, solutions for rendering a nucleic acid susceptible to hybridization, solutions for lysing cells, or solutions for the purification of nucleic acids.

[028] In one embodiment, the invention provides a test kit for monitoring the efficacy of a compound or therapeutic in cancer cells or tissues, comprising an antibody specific for a protein. In certain embodiments, the kit further includes instructions for using the kit. In certain embodiments, the kit may further include solutions for suspending or fixing the cells, detectable tags or labels, solutions for rendering a polypeptide susceptible to the binding of an antibody, solutions for lysing cells, or solutions for the purification of polypeptides.

[029] This invention is also related to methods of identifying biomarkers comprising the steps of selecting a set of biomarker genes from a gene expression profile representing a disease or drug treatment

## DETAILED DESCRIPTION OF THE INVENTION

[030] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, constructs, and reagents described and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[031] It must be noted that as used herein and in the appended claims, the singular forms “a,” “and,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “a gene” is a reference to one or more genes and includes equivalents thereof known to those skilled in the art, and so forth.

[032] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. Any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, and examples of such methods, devices and materials are described below.

[033] All publications and patents mentioned herein are hereby incorporated herein by reference for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in the publications which might be used in connection with the presently described invention. The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

### Definitions

[034] For convenience, the meaning of certain terms and phrases employed in the specification, examples, and appended claims are provided below.

[035] The phrase “a corresponding normal cell of” or “normal cell corresponding to” or “normal counterpart cell of” a diseased cell refers to a normal cell of the same type as that of the diseased cell.

[036] An “address” on an array (e.g., a microarray) refers to a location at which an element, for example, an oligonucleotide, is attached to the solid surface of the array.

[037] The term “agonist,” as used herein, is meant to refer to an agent that mimics or up-regulates (e.g., potentiates or supplements) the bioactivity of a protein. An agonist may be a wild-type protein or derivative thereof having at least one bioactivity of the wild-type protein. An agonist

may also be a compound that up-regulates expression of a gene or which increases at least one bioactivity of a protein. An agonist can also be a compound which increases the interaction of a polypeptide with another molecule, for example, a target peptide or nucleic acid.

[038] "Amplification," as used herein, relates to the production of additional copies of a nucleic acid sequence. For example, amplification may be carried out using polymerase chain reaction (PCR) technologies which are well known in the art. (*see, e.g.*, Dieffenbach, C. W. and G. S. Dveksler (1995) PCR Primer, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y.)

[039] "Antagonist," as used herein, is meant to refer to an agent that down-regulates (e.g., suppresses or inhibits) at least one bioactivity of a protein. An antagonist may be a compound which inhibits or decreases the interaction between a protein and another molecule, for example, a target peptide or enzyme substrate. An antagonist may also be a compound that down-regulates expression of a gene or which reduces the amount of expressed protein present.

[040] The term "antibody," as used herein, is intended to include whole antibodies, for example, of any isotype (IgG, IgA, IgM, IgE, etc.), and includes fragments thereof which are also specifically reactive with a vertebrate (e.g., mammalian) protein. Antibodies may be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. Thus, the term includes segments of proteolytically-cleaved or recombinantly-prepared portions of an antibody molecule that are capable of selectively reacting with a certain protein. Non-limiting examples of such proteolytic and/or recombinant fragments include Fab, F(ab')<sub>2</sub>, Fab', Fv, and single chain antibodies (scFv) containing a V[L] and/or V[H] domain joined by a peptide linker. The scFv's may be covalently or non-covalently linked to form antibodies having two or more binding sites. The subject invention includes polyclonal, monoclonal, or other purified preparations of antibodies and recombinant antibodies.

[041] The terms "array" or "matrix" refer to an arrangement of addressable locations or "addresses" on a device. The locations can be arranged in two-dimensional arrays, three-dimensional arrays, or other matrix formats. The number of locations may range from several to at least hundreds of thousands. Most importantly, each location represents a totally independent reaction site. A "nucleic acid array" refers to an array containing nucleic acid probes, such as oligonucleotides or larger portions of genes. The nucleic acid on the array may be single-stranded. Arrays wherein the probes are oligonucleotides are referred to as "oligonucleotide arrays" or "oligonucleotide chips." A "microarray," also referred to herein as a "biochip" or "biological chip," is an array of regions having a density of discrete regions of, for example, at least about 100/cm<sup>2</sup>, or at least about 1000/cm<sup>2</sup>. The regions in a microarray have typical dimensions, for example, diameters, in the range of between about 10-250  $\mu$ m, and are separated from other regions in the array by about the same distance.

[042] "Biological activity," "bioactivity," "activity," or "biological function," which are used interchangeably, herein mean an effector or antigenic function that is directly or indirectly performed by a polypeptide (whether in its native or denatured conformation), or by any subsequence thereof. Biological activities include binding to polypeptides, binding to other proteins or molecules, activity as a DNA binding protein, as a transcription regulator, ability to bind damaged DNA, etc. A bioactivity can be modulated by directly affecting the subject polypeptide. Alternatively, a bioactivity can be altered by modulating the level of the polypeptide, such as by modulating expression of the corresponding gene.

[043] The term "biological sample," as used herein, refers to a sample obtained from an organism or from components (e.g., cells) of an organism. The sample may be of any biological tissue or fluid. The sample may be a "clinical sample" which is a sample derived from a patient. Such samples include, but are not limited to, sputum, blood, blood cells (e.g., white cells), tissue or fine needle biopsy samples, urine, peritoneal fluid, and pleural fluid, or cells therefrom. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes.

[044] The term "biomarker" or "marker" encompasses a broad range of intra- and extra-cellular events as well as whole-organism physiological changes. Biomarkers may represent essentially any aspect of cell function, for example, but not limited to, levels or rate of production of signaling molecules, transcription factors, metabolites, gene transcripts as well as post-translational modifications of proteins. Biomarkers may include whole genome analysis of transcript levels or whole proteome analysis of protein levels and/or modifications.

[045] A biomarker may also refer to a gene or gene product which is up- or down-regulated in a compound-treated, diseased cell of a subject having the disease compared to an untreated diseased cell. That is, the gene or gene product is sufficiently specific to the treated cell that it may be used, optionally with other genes or gene products, to identify, predict, or detect efficacy of a small molecule. Thus, a biomarker is a gene or gene product that is characteristic of efficacy of a compound in a diseased cell or the response of that diseased cell to treatment by the compound.

[046] A nucleotide sequence is "complementary" to another nucleotide sequence if each of the bases of the two sequences match, that is, are capable of forming Watson-Crick base pairs. The term "complementary strand" is used herein interchangeably with the term "complement." The complement of a nucleic acid strand may be the complement of a coding strand or the complement of a non-coding strand.

[047] "Detection agents of genes" refers to agents that can be used to specifically detect the gene or other biological molecules relating to it, for example, RNA transcribed from the gene or

polypeptides encoded by the gene. Exemplary detection agents are nucleic acid probes, which hybridize to nucleic acids corresponding to the gene, and antibodies.

[048] "Differential gene expression pattern" between cell A and cell B refers to a pattern reflecting the differences in gene expression between cell A and cell B. A differential gene expression pattern may also be obtained between a cell at one time point and a cell at another time point, or between a cell incubated or contacted with a compound and a cell that has not been incubated with or contacted with the compound.

[049] The term "cancer" includes, but is not limited to, solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid, and their distant metastases. The term also includes lymphomas, sarcomas, and leukemias.

[050] Examples of breast cancer include, but are not limited to, invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ*, and lobular carcinoma *in situ*.

[051] Examples of cancers of the respiratory tract include, but are not limited to, small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

[052] Examples of brain cancers include, but are not limited to, brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

[053] Tumors of the male reproductive organs include, but are not limited to, prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to, endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

[054] Tumors of the digestive tract include, but are not limited to, anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

[055] Tumors of the urinary tract include, but are not limited to, bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

[056] Eye cancers include, but are not limited to, intraocular melanoma and retinoblastoma.

[057] Examples of liver cancers include, but are not limited to, hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

[058] Skin cancers include, but are not limited to, squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

[059] Head-and-neck cancers include, but are not limited to, laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

[060] Lymphomas include, but are not limited to, AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

[061] Sarcomas include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

[062] Leukemias include, but are not limited to, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

[063] "A diseased cell of cancer" refers to a cell present in subjects having cancer. That is, a cell which is a modified form of a normal cell and is not present in a subject not having cancer, or a cell which is present in significantly higher or lower numbers in subjects having cancer relative to subjects not having cancer.

[064] The term "equivalent" is understood to include nucleotide sequences encoding functionally equivalent polypeptides. Equivalent nucleotide sequences may include sequences that differ by one or more nucleotide substitutions, additions, or deletions, such as allelic variants; and may, therefore, include sequences that differ from the nucleotide sequence of the nucleic acids referred to in the Tables due to the degeneracy of the genetic code.

[065] The term "expression profile," which is used interchangeably herein with "gene expression profile" and "fingerprint" of a cell refers to a set of values representing mRNA levels of one or more genes in a cell. An expression profile may comprise values representing expression levels of, for example, at least about 10 genes, or at least about 50, 100, 200 or more genes. Expression profiles may also comprise an mRNA level of a gene which is expressed at similar levels in multiple cells and conditions (e.g., a housekeeping gene such as GAPDH). For example, an expression profile of a diseased cell of cancer refers to a set of values representing mRNA levels of 10 or more genes in a diseased cell. In addition, the term "expression profile" may also include a set of values representing one or more protein or polypeptide levels in a cell.

[066] The term "gene" refers to a nucleic acid sequence that comprises control and coding sequences necessary for the production of a polypeptide or precursor. The polypeptide can be encoded by a full length coding sequence or by any portion of the coding sequence. The gene may be derived in whole or in part from any source known to the art, including a plant, a fungus, an animal, a bacterial genome or episome, eukaryotic, nuclear or plasmid DNA, cDNA, viral DNA, or chemically synthesized DNA. A gene may contain one or more modifications in either the coding or the untranslated regions which could affect the biological activity or the chemical structure of

the expression product, the rate of expression, or the manner of expression control. Such modifications include, but are not limited to, mutations, insertions, deletions, and substitutions of one or more nucleotides. The gene may constitute an uninterrupted coding sequence or it may include one or more introns, bound by the appropriate splice junctions.

[067] "Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing. For example, two single-stranded nucleic acids "hybridize" when they form a double-stranded duplex. The region of double-strandedness may include the full-length of one or both of the single-stranded nucleic acids, or all of one single-stranded nucleic acid and a subsequence of the other single-stranded nucleic acid, or the region of double-strandedness may include a subsequence of each nucleic acid. Hybridization also includes the formation of duplexes which contain certain mismatches, provided that the two strands are still forming a double-stranded helix. "Stringent hybridization conditions" refers to hybridization conditions resulting in essentially specific hybridization.

[068] The term "isolated," as used herein, with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term "isolated" as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Moreover, an "isolated nucleic acid" may include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides.

[069] As used herein, the terms "label" and "detectable label" refer to a molecule capable of detection, including, but not limited to, radioactive isotopes, fluorophores, chemiluminescent moieties, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, dyes, metal ions, ligands (e.g., biotin or haptens), and the like. The term "fluorescer" refers to a substance or a portion thereof which is capable of exhibiting fluorescence in the detectable range. Particular examples of labels which may be used in the present invention include fluorescein, rhodamine, dansyl, umbelliferone, Texas red, luminol, NADPH, alpha - beta -galactosidase, and horseradish peroxidase.

[070] The phrase "level of expression" refers to the level of mRNA, as well as pre-mRNA nascent transcript(s), transcript processing intermediates, mature mRNA(s), and degradation products, encoded by a gene in the cell. The phrase "level of expression" also refers to the level of protein or polypeptide in a cell.



[071] As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA) and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs and, as applicable to the embodiment being described, single-stranded (sense or antisense) and double-stranded polynucleotides. Chromosomes, cDNAs, mRNAs, rRNAs, and ESTs are representative examples of molecules that may be referred to as nucleic acids.

[072] The phrase "nucleic acid corresponding to a gene" refers to a nucleic acid that can be used for detecting the gene, for example, a nucleic acid which is capable of hybridizing specifically to the gene.

[073] The phrase "nucleic acid sample derived from RNA" refers to one or more nucleic acid molecules (e.g., RNA or DNA) that may be synthesized from the RNA, and includes DNA produced from methods using PCR (e.g., RT-PCR).

[074] The term "oligonucleotide" as used herein refers to a nucleic acid molecule comprising, for example, from about 10 to about 1000 nucleotides. Oligonucleotides for use in the present invention may be, for example, from about 15 to about 150 nucleotides, or from about 150 to about 1000 in length. The oligonucleotide may be a naturally occurring oligonucleotide or a synthetic oligonucleotide. Oligonucleotides may be prepared by the phosphoramidite method (Beaucage and Carruthers, *Tetrahedron Lett.* 22:1859-62, 1981), or by the triester method (Matteucci, et al., *J. Am. Chem. Soc.* 103:3185, 1981), or by other chemical methods known in the art.

[075] The term "patient" or "subject" as used herein includes mammals (e.g., humans and animals).

[076] The term "percent identical" refers to sequence identity between two amino acid sequences or between two nucleotide sequences. For example, identity between two sequences may be determined by comparing a particular position in each sequence which may be aligned for purposes of comparison. When an equivalent position in the compared sequences is occupied by the same base or amino acid, then the molecules are identical at that position. When the equivalent site is occupied by the same or a similar amino acid residue (e.g., similar in steric and/or electronic nature), then the molecules may be referred to as homologous (similar) at that position.

Expression as a percentage of homology, similarity, or identity refers to a function of the number of identical or similar amino acids at positions shared by the compared sequences. Various alignment algorithms and/or programs may be used including, for example, FASTA, BLAST, or ENTREZ. FASTA and BLAST are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.), and may be used with, for example, default settings. ENTREZ is available through the National Center for Biotechnology Information, National

Library of Medicine, National Institutes of Health, Bethesda, MD. In one embodiment, the percent identity of two sequences may be determined by the GCG program with a gap weight of 1 (e.g., each amino acid gap is weighted as if it were a single amino acid or nucleotide mismatch between the two sequences). Other techniques for alignment are described in *Methods in Enzymology* (vol. 266: Computer Methods for Macromolecular Sequence Analysis (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, California, USA). An alignment program that permits gaps in the sequence may be utilized to align the sequences. For example, the Smith-Waterman is one type of algorithm that permits gaps in sequence alignments (*see, e.g., Meth. Mol. Biol.* 70:173-187, 1997). Also, the GAP program using the Needleman and Wunsch alignment method may be utilized to align sequences. An alternative search strategy uses MPSRCH software, which runs on a MASPAR computer. MPSRCH uses a Smith-Waterman algorithm to score sequences on a massively parallel computer. This approach improves the ability to detect distantly related matches, and is especially tolerant of small gaps and nucleotide sequence errors. Nucleic acid-encoded amino acid sequences may be used to search both protein and DNA databases. Databases with individual sequences are described in *Methods in Enzymology*, ed. Doolittle, *supra*. Databases include, for example, Genbank, EMBL, and DNA Database of Japan (DDBJ).

[077] As used herein, a nucleic acid or other molecule attached to an array is referred to as a "probe" or "capture probe." When an array contains several probes corresponding to one gene, these probes are referred to as a "gene-probe set." A gene-probe set may consist of, for example, about 2 to about 20 probes, from about 2 to about 10 probes, or about 5 probes.

[078] The "profile" of a cell's biological state refers to the levels of various constituents of a cell that are known to change in response to drug treatments and other perturbations of the biological state of the cell. Constituents of a cell include, for example, levels of RNA, levels of protein abundances, or protein activity levels.

[079] The term "protein," "polypeptide," and "peptide" are used interchangeably herein when referring to a gene product.

[080] An expression profile in one cell is "similar" to an expression profile in another cell when the level of expression of the genes in the two profiles are sufficiently similar that the similarity is indicative of a common characteristic, for example, the same type of cell. Accordingly, the expression profiles of a first cell and a second cell are similar when at least 75% of the genes that are expressed in the first cell are expressed in the second cell at a level that is within a factor of two relative to the first cell.

[081] "Small molecule," as used herein, refers to a composition with a molecular weight of less than about 5 kD. Small molecules can be nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids, or other organic or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays of the invention to identify compounds that modulate a bioactivity.

[082] The term "specific hybridization" of a probe to a target site of a template nucleic acid refers to hybridization of the probe predominantly to the target, such that the hybridization signal can be clearly interpreted. As further described herein, such conditions resulting in specific hybridization vary depending on the length of the region of homology, the GC content of the region, and the melting temperature ("T<sub>m</sub>") of the hybrid. Thus, hybridization conditions may vary in salt content, acidity, and temperature of the hybridization solution and the washes.

[083] A "variant" of polypeptide refers to a polypeptide having an amino acid sequence in which one or more amino acid residues is altered. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). A variant may also have "nonconservative" changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be identified using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

[084] The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to that of a particular gene or the coding sequence thereof. This definition may also include, for example, "allelic," "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

*Microarrays for Determining the Level of Expression of Genes*

[085] Generally, determining expression profiles with microarrays involves the following steps: (a) obtaining an mRNA sample from a subject and preparing labeled nucleic acids therefrom (the “target nucleic acids” or “targets”); (b) contacting the target nucleic acids with an array under conditions sufficient for the target nucleic acids to bind to the corresponding probes on the array, for example, by hybridization or specific binding; (c) optional removal of unbound targets from the array; (d) detecting the bound targets, and (e) analyzing the results, for example, using computer based analysis methods. As used herein, “nucleic acid probes” or “probes” are nucleic acids attached to the array, whereas “target nucleic acids” are nucleic acids that are hybridized to the array. Each of these steps is described in more detail below.

[086] Nucleic acid specimens may be obtained from an individual to be tested using either “invasive” or “non-invasive” sampling means. A sampling means is said to be “invasive” if it involves the collection of nucleic acids from within the skin or organs of an animal (including murine, human, ovine, equine, bovine, porcine, canine, or feline animal). Examples of invasive methods include blood collection, semen collection, needle biopsy, pleural aspiration, umbilical cord biopsy, etc. Examples of such methods are discussed by Kim, et al., (J. Virol. 66:3879-3882, 1992); Biswas, et al., (Ann. NY Acad. Sci. 590:582-583, 1990); and Biswas, et al., (J. Clin. Microbiol. 29:2228-2233, 1991).

[087] In contrast, a “non-invasive” sampling means is one in which the nucleic acid molecules are recovered from an internal or external surface of the animal. Examples of such “non-invasive” sampling means include, for example, “swabbing,” collection of tears, saliva, urine, fecal material, sweat or perspiration, hair, etc.

[088] In one embodiment of the present invention, one or more cells from the subject to be tested are obtained and RNA is isolated from the cells. In one embodiment, a sample of peripheral blood leukocytes (PBLs) cells is obtained from the subject. It is also possible to obtain a cell sample from a subject, and then to enrich the sample for a desired cell type. For example, cells may be isolated from other cells using a variety of techniques, such as isolation with an antibody binding to an epitope on the cell surface of the desired cell type. Where the desired cells are in a solid tissue, particular cells may be dissected, for example, by microdissection or by laser capture microdissection (LCM) (*see, e.g.*, Bonner, et al., Science 278:1481, 1997; Emmert-Buck, et al., Science 274:998, 1996; Fend, et al., Am. J. Path. 154:61, 1999; and Murakami, et al., Kidney Int. 58:1346, 2000).

[089] RNA may be extracted from tissue or cell samples by a variety of methods, for example, guanidium thiocyanate lysis followed by CsCl centrifugation (Chirgwin, et al., Biochemistry

18:5294-5299, 1979). RNA from single cells may be obtained as described in methods for preparing cDNA libraries from single cells (*see, e.g.*, Dulac, Curr. Top. Dev. Biol. 36:245, 1998; Jena, et al., J. Immunol. Methods 190:199, 1996).

[090] The RNA sample can be further enriched for a particular species. In one embodiment, for example, poly(A)+ RNA may be isolated from an RNA sample. In particular, poly-T oligonucleotides may be immobilized on a solid support to serve as affinity ligands for mRNA. Kits for this purpose are commercially available, for example, the MessageMaker kit (Life Technologies, Grand Island, NY).

[091] In one embodiment, the RNA population may be enriched for sequences of interest, such as the genes characteristic of human colon tumor tissue (*e.g.*, SEQ ID NOs: 1-96). Enrichment may be accomplished, for example, by primer-specific cDNA synthesis, or multiple rounds of linear amplification based on cDNA synthesis and template-directed *in vitro* transcription (*see, e.g.*, Wang, et al., Proc. Natl. Acad. Sci. USA 86:9717, 1989; Dulac, et al., *supra*; Jena, et al., *supra*).

[092] The population of RNA, enriched or not in particular species or sequences, may be further amplified. Such amplification is particularly important when using RNA from a single cell or a few cells. A variety of amplification methods are suitable for use in the methods of the present invention, including, for example, PCR; ligase chain reaction (LCR) (*see, e.g.*, Wu and Wallace, Genomics 4:560, 1989; Landegren, et al., Science 241:1077, 1988); self-sustained sequence replication (SSR) (*see, e.g.*, Guatelli, et al., Proc. Natl. Acad. Sci. USA 87:1874, 1990); nucleic acid based sequence amplification (NASBA) and transcription amplification (*see, e.g.*, Kwoh, et al., Proc. Natl. Acad. Sci. USA 86:1173, 1989). Methods for PCR technology are well known in the art (*see, e.g.*, PCR Technology: Principles and Applications for DNA Amplification (ed. H. A. Erlich, Freeman Press, N.Y., N.Y., 1992); PCR Protocols: A Guide to Methods and Applications (eds. Innis, et al., Academic Press, San Diego, Calif., 1990); Mattila, et al., Nucleic Acids Res. 19:4967, 1991; Eckert, et al., PCR Methods and Applications 1:17, 1991; PCR (eds. McPherson, et al., IRL Press, Oxford); and U.S. Pat. No. 4,683,202). Methods of amplification are described, for example, by Ohyama, et al., (BioTechniques 29:530, 2000); Luo, et al., (Nat. Med. 5:117, 1999); Hegde, et al., (BioTechniques 29:548, 2000); Kacharina, et al., (Meth. Enzymol. 303:3, 1999); Livesey, et al., Curr. Biol. 10:301, 2000); Spirin, et al., (Invest. Ophthalmol. Vis. Sci. 40:3108, 1999); and Sakai, et al., (Anal. Biochem. 287:32, 2000). RNA amplification and cDNA synthesis may also be conducted in cells *in situ* (*see, e.g.*, Eberwine, et al. Proc. Natl. Acad. Sci. USA 89:3010, 1992).

[093] The target molecules may be labeled to permit detection of hybridization of the target molecules to a microarray. That is, the probe may comprise a member of a signal producing system and thus, is detectable, either directly or through combined action with one or more

additional members of a signal producing system. Examples of directly detectable labels include isotopic and fluorescent moieties incorporated, usually by a covalent bond, into a moiety of the probe, such as a nucleotide monomeric unit (e.g., dNMP of the primer), or a photoactive or chemically active derivative of a detectable label which can be bound to a functional moiety of the probe molecule.

[094] Nucleic acids may be labeled during or after enrichment and/or amplification of RNAs. For example, reverse transcription may be carried out in the presence of a dNTP conjugated to a detectable label, for example, a fluorescently labeled dNTP. In another embodiment, the cDNA or RNA probe may be synthesized in the absence of detectable label and may be labeled subsequently, for example, by incorporating biotinylated dNTPs or rNTP, or some similar means (e.g., photo-cross-linking a psoralen derivative of biotin to RNAs), followed by addition of labeled streptavidin (e.g., phycoerythrin-conjugated streptavidin) or the equivalent.

[095] Fluorescent moieties or labels of interest include coumarin and its derivatives (e.g., 7-amino-4-methylcoumarin, aminocoumarin); bodipy dyes such as Bodipy FL and cascade blue; fluorescein and its derivatives (e.g., fluorescein isothiocyanate, Oregon green); rhodamine dyes (e.g., Texas red, tetramethylrhodamine); eosins and erythrosins; cyanine dyes (e.g., Cy2, Cy3, Cy3.5, Cy5, Cy5.5, Cy7); FluorX, macrocyclic chelates of lanthanide ions (e.g., quantum dye<sup>TM</sup>); fluorescent energy transfer dyes such as thiazole orange-ethidium heterodimer, TOTAB, dansyl, etc. Individual fluorescent compounds which have functionalities for linking to an element desirably detected in an apparatus or assay of the invention, or which may be modified to incorporate such functionalities may also be utilized (*see, e.g.*, Kricka, 1992, *Nonisotopic DNA Probe Techniques*, Academic Press San Diego, Calif.).

[096] Chemiluminescent labels include luciferin and 2,3-dihydrophthalazinediones, for example, luminol.

[097] Labels may also be members of a signal producing system that act in concert with one or more additional members of the same system to provide a detectable signal. Illustrative of such labels are members of a specific binding pair, such as ligands, for example, biotin, fluorescein, digoxigenin, antigen, polyvalent cations, chelator groups and the like. Members may specifically bind to additional members of the signal producing system, and the additional members may provide a detectable signal either directly or indirectly, for example, an antibody conjugated to a fluorescent moiety or an enzymatic moiety capable of converting a substrate to a chromogenic product (e.g., alkaline phosphatase conjugate antibody and the like).

[098] Additional labels of interest include those that provide a signal only when the probe with which it is associated is specifically bound to a target molecule. Such labels include "molecular

beacons" as described in Tyagi and Kramer (Nature Biotech. 14:303, 1996) and EP 0 070 685 B1. Other labels of interest include those described in U.S. Patent No. 5,563,037; WO 97/17471; and WO 97/17076.

[099] In other embodiments, the target nucleic acid may not be labeled. In this case, hybridization may be determined, for example, by plasmon resonance (*see, e.g.*, Thiel, et al., Anal. Chem. 69:4948, 1997):

[100] In one embodiment, a plurality (e.g., 2, 3, 4, 5, or more) of sets of target nucleic acids are labeled and used in one hybridization reaction ("multiplex" analysis). For example, one set of nucleic acids may correspond to RNA from one cell and another set of nucleic acids may correspond to RNA from another cell. The plurality of sets of nucleic acids may be labeled with different labels, for example, different fluorescent labels (e.g., fluorescein and rhodamine) which have distinct emission spectra so that they can be distinguished. The sets may then be mixed and hybridized simultaneously to one microarray (*see, e.g.*, Shena, et al., Science 270:467-470, 1995).

[101] Examples of distinguishable labels for use when hybridizing a plurality of target nucleic acids to one array are well known in the art and include: two or more different emission wavelength fluorescent dyes such as Cy3 and Cy5; combination of fluorescent proteins and dyes such as phicoerythrin and Cy5; two or more isotopes with different energy of emission such as  $^{32}\text{P}$  and  $^{33}\text{P}$ ; gold or silver particles with different scattering spectra; labels which generate signals under different treatment conditions such as temperature, pH, treatment with additional chemical agents, etc.; or generate signals at different time points after treatment. Using one or more enzymes for signal generation allows for the use of an even greater variety of distinguishable labels, based on different substrate specificity of enzymes (e.g., alkaline phosphatase/peroxidase).

[102] The quality of labeled nucleic acids may be evaluated prior to hybridization to an array. In one embodiment, the GeneChip<sup>®</sup> Test3 Array from Affymetrix (Santa Clara, CA) may be used for that purpose. This array contains probes representing a subset of characterized genes from several organisms including mammals. Thus, the quality of a labeled nucleic acid sample can be determined by hybridization of a fraction of the sample to an array.

[103] Microarrays for use according to the invention include one or more probes of genes characteristic of human colon tumor tissue. In one embodiment, the microarray comprises one or more probes corresponding to one or more of genes selected from the group consisting of genes which are up-regulated in cancer and genes which are down-regulated in cancer. The microarray may comprise probes corresponding to, for example, at least 10, at least 20, at least 50, at least 100, or at least 1000 genes characteristic of human colon tumor tissue. The microarray may comprise probes corresponding to each gene listed in the Tables.

[104] There may be one or more than one probe corresponding to each gene on a microarray. For example, a microarray may contain from 2 to 20 probes corresponding to one gene or about 5 to 10. The probes may correspond to the full-length RNA sequence or complement thereof of genes characteristic of human colon tumor tissue, or the probe may correspond to a portion thereof, which portion is of sufficient length to permit specific hybridization. Such probes may comprise from about 50 nucleotides to about 100, 200, 500, or 1000 nucleotides or more than 1000 nucleotides. As further described herein, microarrays may contain oligonucleotide probes, consisting of about 10 to 50 nucleotides, about 15 to 30 nucleotides, or about 20-25 nucleotides. The probes may be single-stranded and will have sufficient complementarity to its target to provide for the desired level of sequence specific hybridization.

[105] Typically, the arrays used in the present invention will have a site density of greater than 100 different probes per  $\text{cm}^2$ . The arrays may have a site density of, for example, greater than  $500/\text{cm}^2$ , greater than about  $1000/\text{cm}^2$ , or greater than about  $10,000/\text{cm}^2$ . The arrays may have, for example, more than about 100 different probes on a single substrate, more than about 1000 different probes, more than about 10,000 different probes, or more than about 100,000 different probes on a single substrate.

[106] A number of different microarray configurations and methods for their production are known to those of skill in the art and are disclosed in U.S. Patent Nos: 5,242,974; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,436,327; 5,445,934; 5,556,752; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,436,327; 5,472,672; 5,527,681; 5,529,756; 5,545,531; 5,554,501; 5,561,071; 5,571,639; 5,593,839; 5,624,711; 5,700,637; 5,744,305; 5,770,456; 5,770,722; 5,837,832; 5,856,101; 5,874,219; 5,885,837; 5,919,523; 6,022,963; 6,077,674; and 6,156,501; Shena, et al., Tibtech 16:301, 1998; Duggan, et al., Nat. Genet. 21:10, 1999; Bowtell, et al., Nat. Genet. 21:25, 1999; Lipshutz, et al., 21 Nature Genet. 20-24, 1999; Blanchard, et al., 11 Biosensors and Bioelectronics, 687-90, 1996; Maskos, et al., 21 Nucleic Acids Res. 4663-69, 1993; Hughes, et al., Nat. Biotechnol. 19:342, 2001; the disclosures of which are herein incorporated by reference. Patents describing methods of using arrays in various applications include: U.S. Pat. Nos. 5,143,854; 5,288,644; 5,324,633; 5,432,049; 5,470,710; 5,492,806; 5,503,980; 5,510,270; 5,525,464; 5,547,839; 5,580,732; 5,661,028; 5,848,659; and 5,874,219; the disclosures of which are herein incorporated by reference.

[107] Arrays may include control and reference nucleic acids. Control nucleic acids include, for example, prokaryotic genes such as bioB, bioC and bioD, cre from P1 bacteriophage or polyA controls, such as dap, lys, phe, thr, and trp. Reference nucleic acids allow the normalization of results from one experiment to another and the comparison of multiple experiments on a



quantitative level. Exemplary reference nucleic acids include housekeeping genes of known expression levels, for example, GAPDH, hexokinase, and actin.

[108] In one embodiment, an array of oligonucleotides may be synthesized on a solid support. Exemplary solid supports include paper, membranes, filters, pins, glass, plastics, polymers, metals, metalloids, ceramics, organics, etc. Using chip masking technologies and photoprotective chemistry, it is possible to generate ordered arrays of nucleic acid probes. These arrays, which are known, for example, as "DNA chips" or very large scale immobilized polymer arrays ("VLSIPS<sup>TM</sup>" arrays), may include millions of defined probe regions on a substrate having an area of about 1 cm<sup>2</sup> to several cm<sup>2</sup>, thereby incorporating from a few to millions of probes (*see, e.g.*, U.S. Patent No. 5,631,734).

[109] A nucleic acid probe may be at least, for example, about 10, 15, 20, 25, 30, 50, 100 or more nucleotides, and may comprise the full-length gene. For example, probes may be those that hybridize specifically to the genes listed in the Tables.

[110] Nucleic acid probes may be obtained, for example, by PCR amplification of gene segments from genomic, cDNA (e.g., RT-PCR), or cloned sequences. cDNA probes may be prepared according to methods known in the art and further described herein, for example, by reverse-transcription PCR (RT-PCR) of RNA using sequence specific primers. Sequences of genes or cDNA from which probes are generated may be obtained, for example, from GenBank, other public databases, or publications.

[111] Oligonucleotide probes may also be synthesized by standard methods known in the art, for example, by automated DNA synthesizer or any other chemical method. As an example, phosphorothioate oligonucleotides may be synthesized by the method of Stein, et al., (Nucl. Acids Res. 16:3209, 1988), and methylphosphonate oligonucleotides may be prepared by controlled pore glass polymer supports (*see, e.g.*, Sarin, et al., Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451, 1988). In another embodiment, the oligonucleotide may be a 2'-methylribonucleotide (Inoue, et al., Nucl. Acids Res. 15:6131-6148, 1987), or a chimeric RNA-DNA analog (Inoue, et al., FEBS Lett. 215:327-330, 1987).

[112] Nucleic acid probes may be natural nucleic acids or chemically modified nucleic acids (e.g., composed of nucleotide analogs); however, the probes should possess activated hydroxyl groups compatible with the linking chemistry. The protective groups may be photolabile, or the protective groups may be labile under certain chemical conditions (e.g., acid). The surface of the solid support may contain a composition that generates acids upon exposure to light. Thus, exposure of a region of the substrate to light generates acids in that region that remove the protective groups in the exposed region. Also, the synthesis method may use 3'-protected 5'-O-phosphoramidite-

activated deoxynucleoside. In this case, the oligonucleotide is synthesized in the 5' to 3' direction, which results in a free 5' end.

[113] In one embodiment of the present invention, oligonucleotides of an array may be synthesized using a 96-well automated multiplex oligonucleotide synthesizer (A.M.O.S.) that is capable of producing thousands of oligonucleotides (*see, e.g.*, Lashkari, et al., Proc. Natl. Acad. Sci. USA 93: 7912, 1995).

[114] To compare expression levels, labeled nucleic acids may be contacted with the array under conditions sufficient for binding between the target nucleic acid and the probe on the array. In one embodiment, the hybridization conditions may be selected to provide for the desired level of hybridization specificity; that is, conditions sufficient for hybridization to occur between the labeled nucleic acids and probes on the microarray.

[115] Hybridization may be carried out in conditions permitting essentially specific hybridization. The length and GC content of the nucleic acid will determine the thermal melting point and thus, the hybridization conditions necessary for obtaining specific hybridization of the probe to the target nucleic acid. These factors are well known to a person of skill in the art, and may also be tested in assays. An extensive guide to nucleic acid hybridization may be found in Tijssen, et al. (Laboratory Techniques in Biochemistry and Molecular Biology, Vol. 24: Hybridization With Nucleic Acid Probes, P. Tijssen, ed. Elsevier, N.Y., (1993)). Generally, stringent conditions may be selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Highly stringent conditions may be selected to be equal to the  $T_m$  point for a particular probe. Sometimes the term "dissociation temperature" ( $T_d$ ) is used to define the temperature at which at least half of the probe dissociates from a perfectly matched target nucleic acid. In any case, a variety of techniques for estimating the  $T_m$  or  $T_d$  are available, and generally are described in Tijssen, *supra*. Typically, G-C base pairs in a duplex are estimated to contribute about 3°C to the  $T_m$ , while A-T base pairs are estimated to contribute about 2°C, up to a theoretical maximum of about 80-100°C. However, more sophisticated models of  $T_m$  and  $T_d$  are available in which G-C stacking interactions, solvent effects, the desired assay temperature, and the like are taken into account.

[116] In one embodiment, non-specific binding or background signal may be reduced by the use of a detergent (e.g., C-TAB) or a blocking reagent (e.g., sperm DNA, cot-1 DNA, etc.) during the hybridization. In another embodiment, the hybridization may be performed in the presence of about 0.5 mg/ml DNA (e.g., herring sperm DNA). The use of blocking agents in hybridization is well known to those of skill in the art (*see, e.g.*, Tijssen, *supra*).

[117] If the target sequences are detected using the same label, different arrays may be employed for each physiological source or the same array may be screened multiple times. The above methods may be varied to provide for multiplex analysis by employing different and distinguishable labels for the different target populations (e.g., different physiological sources). According to this multiplex method, the same array may be used at the same time for each of the different target populations.

[118] The methods described above result in the production of hybridization patterns of labeled target nucleic acids on the array surface. The resultant hybridization patterns of labeled nucleic acids may be visualized or detected in a variety of ways, with the particular manner of detection selected based on the particular label of the target nucleic acid. Representative detection means include scintillation counting, autoradiography, fluorescence measurement, colorimetric measurement, light emission measurement, light scattering, and the like.

[119] One such method of detection utilizes an array scanner that is commercially available (Affymetrix, Santa Clara, CA), for example, the 417<sup>TM</sup> Arrayer, the 418<sup>TM</sup> Array Scanner, or the Agilent GeneArray<sup>TM</sup> Scanner. This scanner is controlled from a system computer with an interface and easy-to-use software tools. The output may be directly imported into or directly read by a variety of software applications. Scanning devices are described in, for example, U.S. Patent Nos. 5,143,854 and 5,424,186.

[120] For fluorescent labeled probes, the fluorescence emissions at each site of a transcript array may be, for example, detected by scanning confocal laser microscopy. Alternatively, a laser may be used that allows simultaneous specimen illumination at wavelengths specific to the two fluorophores and emissions from the two fluorophores may be analyzed simultaneously (*see, e.g.*, Shalon, et al., *Genome Res.* 6:639-645, 1996). In one embodiment, the arrays may be scanned with a laser fluorescent scanner with a computer controlled X-Y stage and a microscope objective. Fluorescence laser scanning devices are described in Shalon, et al., *supra*.

[121] Following the data gathering operation, the data will typically be reported to a data analysis operation. To facilitate the sample analysis operation, the data obtained by the reader from the device may be analyzed using a digital computer. Typically, the computer will be appropriately programmed for receipt and storage of the data from the device, as well as for analysis and reporting of the data gathered, for example, subtraction of the background, deconvolution of multi-color images, flagging or removing artifacts, verifying that controls have performed properly, normalizing the signals, interpreting fluorescence data to determine the amount of hybridized target, normalization of background and single base mismatch hybridizations, and the like.

[122] In one embodiment, a system comprises a search function that allows one to search for specific patterns, for example, patterns relating to differential gene expression, for example, between the expression profile of a cancer cell and the expression profile of a counterpart normal cell in a subject. A system may also allow one to search for patterns of gene expression between more than two samples.

[123] Various algorithms are available for analyzing gene expression profile data, for example, the type of comparisons to perform. In certain embodiments, it is desirable to group genes that are co-regulated. This allows for the comparison of large numbers of profiles. One embodiment for identifying such groups of genes involves clustering algorithms (for reviews of clustering algorithms, *see, e.g.*, Fukunaga, 1990, Statistical Pattern Recognition, 2nd Ed., Academic Press, San Diego; Everitt, 1974, Cluster Analysis, London: Heinemann Educ. Books; Hartigan, 1975, Clustering Algorithms, New York: Wiley; Sneath and Sokal, 1973, Numerical Taxonomy, Freeman; Anderberg, 1973, Cluster Analysis for Applications, Academic Press: New York).

[124] Clustering may be based on other characteristics of the genes, for example, their level of expression (*see, e.g.*, U.S. Patent No. 6,203,987), or permit clustering of time curves (*see, e.g.* U.S. Patent No. 6,263,287). Examples of clustering algorithms include K-means clustering and hierarchical clustering. Clustering may also be achieved by visual inspection of gene expression data using a graphical representation of the data (e.g. a "heat map"). An example of software which contains clustering algorithms and a means to graphically represent gene expression data is Spotfire DecisionSite (Spotfire, Inc., Somerville, Massachusetts and Göteborg, Sweden).

[125] Comparison of the expression levels of one or more genes characteristic of human colon tumor tissue with reference expression levels, for example, expression levels in diseased cells of cancer or in normal counterpart cells, may be conducted using computer systems. In one embodiment, expression levels may be obtained from two cells and these two sets of expression levels may be introduced into a computer system for comparison. In another embodiment, one set of expression levels is entered into a computer system for comparison with values that are already present in the computer system, or in computer-readable form that is then entered into the computer system.

[126] In one embodiment, the computer system may also contain a database comprising values representing levels of expression of one or more genes characteristic of human colon tumor tissue. The database may contain one or more expression profiles of genes characteristic of human colon tumor tissue in different cells.

[127] In another embodiment, the invention provides a computer-readable form of the gene expression profile data, or of values corresponding to the level of expression of at least one gene

characteristic of cancer in a diseased cell. The values may be mRNA expression levels obtained from experiments, for example, microarray analysis. The values may also be mRNA levels normalized relative to a reference gene whose expression is constant in numerous cells under numerous conditions (e.g., GAPDH). In other embodiments, the values in the computer may be ratios of, or differences between, normalized or non-normalized mRNA levels in different samples.

[128] In one embodiment, the expression data of a cell of a subject treated *in vitro* or *in vivo* with the drug is entered into a computer and the computer is instructed to compare the data entered to the data in the computer, and to provide results indicating whether the expression data input into the computer are more similar to those of a cell of a subject that is responsive to the drug or more similar to those of a cell of a subject that is not responsive to the drug. Thus, the results indicate whether the subject is likely to respond to the treatment with the drug or unlikely to respond to it.

[129] The invention also provides a machine-readable or computer-readable medium including program instructions for performing the following steps: (i) comparing a plurality of values corresponding to expression levels of one or more genes characteristic of human colon tumor tissue in a query cell with a database including records comprising reference expression or expression profile data of one or more reference cells and an annotation of the type of cell; and (ii) indicating to which cell the query cell is most similar based on similarities of expression profiles. The reference cells may be cells from subjects at different stages of cancer. The reference cells may also be cells from subjects responding or not responding to a particular drug treatment and optionally incubated *in vitro* or *in vivo* with the drug.

[130] The reference cells may also be cells from subjects responding or not responding to several different treatments, and the computer system indicates a preferred treatment for the subject. Accordingly, the invention provides a method for selecting a therapy for a patient having cancer, the method comprising: (i) providing the level of expression of one or more genes characteristic of human colon tumor tissue in a diseased cell of the patient; (ii) providing a plurality of reference profiles, each associated with a therapy, wherein the subject expression profile and each reference profile has a plurality of values, each value representing the level of expression of a gene characteristic of cancer; and (iii) selecting the reference profile most similar to the subject expression profile, to thereby select a therapy for said patient. In one embodiment, step (iii) is performed by a computer. The most similar reference profile may be selected by weighing a comparison value of the plurality using a weight value associated with the corresponding expression data.

[131] The relative abundance of an mRNA in two biological samples may be scored as a perturbation and its magnitude determined (i.e., the abundance is different in the two sources of

mRNA tested), or as not perturbed (i.e., the relative abundance is the same). In various embodiments, a difference between the two sources of RNA of at least a factor of about 25% (RNA from one source is 25% more abundant in one source than the other source), more usually about 50%, even more often by a factor of about 2 (twice as abundant), 3 (three times as abundant) or 5 (five times as abundant) is scored as a perturbation. Perturbations may be used by a computer for calculating and expression comparisons.

#### *Drug Design Using Microarrays*

[132] The invention also provides methods for designing and optimizing drugs for cancer. In one embodiment, compounds may be screened by comparing the expression level of one or more genes characteristic of human colon tumor tissue following incubation of a diseased cell of cancer or similar cell with the test compound. In another embodiment, the expression level of the genes may be determined using microarrays, and comparing the gene expression profile of a cell in response to the test compound with the gene expression profile of a normal cell corresponding to a diseased cell of cancer (a "reference profile"). In a further embodiment, the expression profile may also be compared to that of a diseased cell of cancer. The comparisons may be done by introducing the gene expression profile data of the cell treated with drug into a computer system comprising reference gene expression profiles, which are stored in a computer readable form, using appropriate algorithms. Test compounds may be screened for those that alter the level of expression of genes characteristic of human colon tumor tissue. Such compounds, that is, compounds which are capable of normalizing the expression of essentially all genes characteristic of human colon tumor tissue, are candidate therapeutics.

[133] The efficacy of the compounds may then be tested in additional *in vitro* and *in vivo* assays, and in animal models (e.g., xenograft model). The test compound may be administered to the test animal, and one or more symptoms of the disease may be monitored for improvement of the condition of the animal. Expression of one or more genes characteristic of human colon tumor tissue may also be measured before and after administration of the test compound to the animal. A normalization of the expression of one or more of these genes is indicative of the efficiency of the compound for treating cancer in the animal.

[134] In the clinical setting, obtaining human-derived samples of tissue exhibiting cancer may be difficult, if not prohibitive. Therefore, identification of gene expression changes indicative of efficacy of a therapeutic compound may be determined in a more easily accessible, surrogate cell population, for example, peripheral blood leukocytes (PBLs). This method may be performed either in a human or animal model system. In one embodiment, a test compound may be administered to the test animal (either normal or cancer-containing) at the same doses that have been observed to be efficacious in treating cancer in that animal model. Blood may be drawn from

the animal at various time points (e.g., 1, 4, 7, and 24 hours following the first, mid-point, and last day of a regimen of multiple day dosing). Animals dosed with vehicle may be used as controls. RNA may be isolated from PBLs, and can be used to generate probes for hybridization to microarrays. The hybridization results may then be analyzed using computer programs and databases, as described above. The resulting expression profile may be compared directly to the analogous profile from the treated cancer tissue for similarities or simply correlated with efficacy (e.g., in terms of doses and time points) in the animal model.

[135] In another embodiment, human blood may be treated *ex vivo* with a therapeutic compound at a dose consistent with the therapeutic dose in the animal model, or at a dose that is consistent with known plasma levels of the therapeutic dose in the animal model. The blood may be treated (e.g., rocking at 37°C) with the therapeutic compound immediately, or after some period of incubation time (e.g., 24 hours) to allow for gene expression to re-equilibrate after the blood draw. The blood may also be treated with the therapeutic compound for various timepoints (e.g., 4 and 24 hours), and then PBL RNA isolated and used to create a probe for hybridization to a microarray. A compound solubilization agent (e.g., DMSO) may be used as a control. The resulting expression profile may be compared directly to the analogous profile from the treated cancer tissue for similarities or simply correlated with efficacy (e.g., in terms of doses and time points) in the animal model.

[136] The toxicity of the candidate therapeutic compound may be evaluated, for example, by determining whether the compound induces the expression of genes known to be associated with a toxic response. Expression of such toxicity related genes may be determined in different cell types, for example, those that are known to express the genes. In fact, alterations in gene expression may serve as a more sensitive marker of human toxicity than routine preclinical safety studies. In one method, microarrays may be used for detecting changes in the expression of genes known to be associated with a toxic response. It may be possible to perform proof of concept studies demonstrating that changes in gene expression levels may predict toxic events that were not identified by routine preclinical safety testing (*see, e.g.,* Huang, et al., Toxicol. Sci. 63:196-207, 2001; Waring, et al., Toxicol. Appl. Pharmacol. 175:28-42, 2001).

[137] Drug screening may be performed by adding a test compound to a sample of cells, and monitoring the effect. A parallel sample which does not receive the test compound may also be monitored as a control. The treated and untreated cells are then compared by any suitable phenotypic criteria, including but not limited to microscopic analysis, viability testing, ability to replicate, histological examination, the level of a particular RNA or polypeptide associated with the cells, the level of enzymatic activity expressed by the cells or cell lysates, and the ability of the

cells to interact with other cells or compounds. Differences between treated and untreated cells indicates effects attributable to the test compound.

[138] Desirable effects of a test compound include an effect on any phenotype that was conferred by the cancer-associated marker nucleic acid sequence. Examples include a test compound that limits the overabundance of mRNA, limits production of the encoded protein, or limits the functional effect of the protein. The effect of the test compound would be apparent when comparing results between treated and untreated cells.

#### *Diagnostic and Prognostic Assays*

[139] The present invention provides nucleic acid sequences which are differentially regulated in cancer, and a method for identifying such sequences. The present invention provides a method for identifying a nucleotide sequence which is differentially regulated in a subject with cancer, comprising: hybridizing a nucleic acid sample corresponding to RNA obtained from the subject to a nucleic acid sample comprising one or more nucleic acid molecules of known identity; and measuring the hybridization of the nucleic acid sample to the one or more nucleic acid molecules of known identity, wherein a difference in the hybridization of the nucleic acid sample to the one or more nucleic acid molecules of known identity relative to a nucleic acid sample obtained from a subject without cancer is indicative of the differential expression of the nucleotide sequence in a subject with cancer.

[140] Generally, the present invention provides a method for identifying nucleic acid sequences which are differentially regulated in a subject with cancer comprising isolating messenger RNA from a subject, generating cRNA from the mRNA sample, hybridizing the cRNA to a microarray comprising a plurality of nucleic acid molecules stably associated with discrete locations on the array, and identifying patterns of hybridization of the cRNA to the array. According to the present invention, a nucleic acid molecule which hybridizes to a given location on the array is said to be differentially regulated if the hybridization signal is, for example, at least two-fold higher or lower than the hybridization signal at the same location on an identical array hybridized with a nucleic acid sample obtained from a subject that does not have cancer.

[141] Expression patterns may be used to derive a panel of biomarkers that can be used to predict the efficacy of drug treatment in the patients. The biomarkers may consist of gene expression levels from microarray experiments on RNA isolated from biological samples, RNA isolated from frozen samples of tumor biopsies, or mass spectrometry-derived protein masses in the serum.

[142] Although the precise mechanism for data analysis will depend upon the exact nature of the data, a typical procedure for developing a panel of biomarkers is as follows. The data (gene expression levels or mass spectra) are collected for each patient prior to treatment. As the study



progresses, the patients are classified according to their response to the drug treatment; either as efficacious or non-efficacious. Multiple levels of efficacy can be accommodated in a data model, but a binary comparison is considered optimal, particularly if the patient population is less than several hundred. Assuming adequate numbers of patients in each class, the protein and/or gene expression data may be analyzed by a number of techniques known in the art. Many of the techniques are derived from traditional statistics as well from the field of machine learning. These techniques serve two purposes:

1. Reduce the dimensionality of data - In the case of mass spectra or gene expression microarrays, data is reduced from many thousands of individual data points to about three to ten. The reduction is based upon the predictive power of the data points when taken as a set.
2. Training - These three to ten data points are then used to train multiple machine learning algorithms which then "learn" to recognize, in this case, patterns of protein masses or gene expression which distinguish efficacious drug treatment from non-efficacious. All patient samples can be used to train the algorithms.

[143] The resulting trained algorithms are then tested in order to measure their predictive power. Typically, when less than many hundreds of training examples are available, some form of cross-validation is performed. To illustrate, consider a ten-fold cross validation. In this case, patient samples are randomly assigned to one of ten bins. In the first round of validation the samples in nine of the bins are used for training and the remaining samples in the tenth bin are used to test the algorithm. This is repeated an additional nine times, each time leaving out the samples in a different bin for testing. The results (correct predictions and errors) from all ten rounds are combined and the predictive power is then assessed. Different algorithms, as well as different panels, may be compared in this way for this study. The "best" algorithm/panel combination will then be selected. This "smart" algorithm may then be used in future studies to select the patients that are most likely to respond to treatment.

[144] Many algorithms benefit from additional information taken for the patients. For example, gender or age could be used to improve predictive power. Also, data transformations such as normalization and smoothing may be used to reduce noise. Because of this, a large number of algorithms may be trained using many different parameters in order to optimize the outcome. If predictive patterns exist in the data, it is likely that an optimal, or near-optimal, "smart" algorithm can be developed. If more patient samples become available, the algorithm can be retrained to take advantage of the new data.

[145] As an example using mass spectrometry, plasma may be applied to a hydrophobic SELDI-target, washed extensively in water, and analyzed by the SELDI-ToF mass spectrometer. This may be repeated on 100 or more patient samples. The protein profiles resulting from the intensities of

some 16,000  $m/z$  values in each sample would be statistically analyzed in order to identify sets of specific  $m/z$  values that are predictive of drug efficacy. Identical experiments using other SELDI-targets, such as ion-exchange or IMAC surfaces, could also be conducted. These will capture different subsets of the proteins present in plasma. Furthermore, the plasma may be denatured and prefractionated prior to application onto the SELDI target.

[146] The present invention provides methods for determining whether a subject is at risk for developing a disease or condition characterized by unwanted cell proliferation by detecting biomarkers, that is, nucleic acids and/or polypeptide markers for cancer.

[147] In clinical applications, human tissue samples may be screened for the presence and/or absence of biomarkers identified herein. Such samples could consist of needle biopsy cores, surgical resection samples, lymph node tissue, or serum. For example, these methods include obtaining a biopsy, which is optionally fractionated by cryostat sectioning to enrich tumor cells to about 80% of the total cell population. In certain embodiments, nucleic acids extracted from these samples may be amplified using techniques well known in the art. The levels of selected markers detected would be compared with statistically valid groups of metastatic, non-metastatic malignant, benign, or normal tissue samples.

[148] In one embodiment, the diagnostic method comprises determining whether a subject has an abnormal mRNA and/or protein level of the biomarkers, such as by Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), *in situ* hybridization, immunoprecipitation, Western blot hybridization, or immunohistochemistry. According to the method, cells may be obtained from a subject and the levels of the biomarkers, protein, or mRNA level, are determined and compared to the level of these markers in a healthy subject. An abnormal level of the biomarker polypeptide or mRNA levels is likely to be indicative of cancer.

[149] In one embodiment, the method comprises using a nucleic acid probe to determine the presence of cancerous cells in a tissue from a patient. Specifically, the method comprises:

1. providing a nucleic acid probe comprising a nucleotide sequence, for example, at least 10, 15, 25 or 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a nucleic acid sequence and is differentially expressed in tumors cells;
2. obtaining a tissue sample from a patient potentially comprising cancerous cells;
3. providing a second tissue sample containing cells substantially all of which are non-cancerous;

4. contacting the nucleic acid probe under stringent conditions with RNA of each of said first and second tissue samples (e.g., in a Northern blot or *in situ* hybridization assay); and
5. comparing (a) the amount of hybridization of the probe with RNA of the first tissue sample, with (b) the amount of hybridization of the probe with RNA of the second tissue sample; wherein a statistically significant difference in the amount of hybridization with the RNA of the first tissue sample as compared to the amount of hybridization with the RNA of the second tissue sample is indicative of the presence of cancerous cells in the first tissue sample.

[150] In one aspect, the method comprises *in situ* hybridization with a probe derived from a given marker nucleic acid sequence. The method comprises contacting the labeled hybridization probe with a sample of a given type of tissue potentially containing cancerous or pre-cancerous cells as well as normal cells, and determining whether the probe labels some cells of the given tissue type to a degree significantly different (e.g., by at least a factor of two, or at least a factor of five, or at least a factor of twenty, or at least a factor of fifty) than the degree to which it labels other cells of the same tissue type.

[151] Also within the invention is a method of determining the phenotype of a test cell from a given human tissue, for example, whether the cell is (a) normal, or (b) cancerous or precancerous, by contacting the mRNA of a test cell with a nucleic acid probe, for example, at least about 10, 15, 25, or 40 nucleotides, and up to all or nearly all of a sequence which is complementary to a portion of the coding sequence of a nucleic acid sequence, and which is differentially expressed in tumor cells as compared to normal cells of the given tissue type; and determining the approximate amount of hybridization of the probe to the mRNA, an amount of hybridization either more or less than that seen with the mRNA of a normal cell of that tissue type being indicative that the test cell is cancerous or pre-cancerous.

[152] Alternatively, the above diagnostic assays may be carried out using antibodies to detect the protein product encoded by the marker nucleic acid sequence. Accordingly, in one embodiment, the assay would include contacting the proteins of the test cell with an antibody specific for the gene product of a nucleic acid, the marker nucleic acid being one which is expressed at a given control level in normal cells of the same tissue type as the test cell, and determining the approximate amount of immunocomplex formation by the antibody and the proteins of the test cell, wherein a statistically significant difference in the amount of the immunocomplex formed with the proteins of a test cell as compared to a normal cell of the same tissue type is an indication that the test cell is cancerous or pre-cancerous.

[153] The method for producing polyclonal and/or monoclonal antibodies which specifically bind to polypeptides useful in the present invention is known to those of skill in the art and may be found in, for example, Dymecki, et al., (J. Biol. Chem. 267:4815, 1992); Boersma & Van Leeuwen, (J. Neurosci. Methods 51:317, 1994); Green, et al., (Cell 28:477, 1982); and Arnheiter, et al., (Nature 294:278, 1981).

[154] Another such method includes the steps of: providing an antibody specific for the gene product of a marker nucleic acid sequence, the gene product being present in cancerous tissue of a given tissue type at a level more or less than the level of the gene product in non-cancerous tissue of the same tissue type; obtaining from a patient a first sample of tissue of the given tissue type, which sample potentially includes cancerous cells; providing a second sample of tissue of the same tissue type (which may be from the same patient or from a normal control, e.g. another individual or cultured cells), this second sample containing normal cells and essentially no cancerous cells; contacting the antibody with protein (which may be partially purified, in lysed but unfractionated cells, or *in situ*) of the first and second samples under conditions permitting immunocomplex formation between the antibody and the marker nucleic acid sequence product present in the samples; and comparing (a) the amount of immunocomplex formation in the first sample, with (b) the amount of immunocomplex formation in the second sample, wherein a statistically significant difference in the amount of immunocomplex formation in the first sample less as compared to the amount of immunocomplex formation in the second sample is indicative of the presence of cancerous cells in the first sample of tissue.

[155] The subject invention further provides a method of determining whether a cell sample obtained from a subject possesses an abnormal amount of marker polypeptide which comprises (a) obtaining a cell sample from the subject, (b) quantitatively determining the amount of the marker polypeptide in the sample so obtained, and (c) comparing the amount of the marker polypeptide so determined with a known standard, so as to thereby determine whether the cell sample obtained from the subject possesses an abnormal amount of the marker polypeptide. Such marker polypeptides may be detected by immunohistochemical assays, dot-blot assays, ELISA, and the like.

[156] Immunoassays are commonly used to quantitate the levels of proteins in cell samples, and many other immunoassay techniques are known in the art. The invention is not limited to a particular assay procedure, and therefore, is intended to include both homogeneous and heterogeneous procedures. Exemplary immunoassays which may be conducted according to the invention include fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), nephelometric inhibition immunoassay (NIA), enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA). An indicator moiety, or label

group, may be attached to the subject antibodies and is selected so as to meet the needs of various uses of the method which are often dictated by the availability of assay equipment and compatible immunoassay procedures. General techniques to be used in performing the various immunoassays noted above are known to those of ordinary skill in the art.

[157] In another embodiment, the level of the encoded product, or alternatively the level of the polypeptide, in a biological fluid (e.g., blood or urine) of a patient may be determined as a way of monitoring the level of expression of the marker nucleic acid sequence in cells of that patient. Such a method would include the steps of obtaining a sample of a biological fluid from the patient, contacting the sample (or proteins from the sample) with an antibody specific for an encoded marker polypeptide, and determining the amount of immune complex formation by the antibody, with the amount of immune complex formation being indicative of the level of the marker encoded product in the sample. This determination is particularly instructive when compared to the amount of immune complex formation by the same antibody in a control sample taken from a normal individual or in one or more samples previously or subsequently obtained from the same person.

[158] In another embodiment, the method may be used to determine the amount of marker polypeptide present in a cell, which in turn may be correlated with progression of a hyperproliferative disorder. The level of the marker polypeptide may be used predictively to evaluate whether a sample of cells contains cells which are, or are predisposed towards becoming, transformed cells. Moreover, the subject method may be used to assess the phenotype of cells which are known to be transformed, the phenotyping results being useful in planning a particular therapeutic regimen. For example, very high levels of the marker polypeptide in sample cells is a powerful diagnostic and prognostic marker for a cancer. The observation of marker polypeptide levels may be utilized in decisions regarding, for example, the use of more aggressive therapies.

[159] As set out above, one aspect of the present invention relates to diagnostic assays for determining, in the context of cells isolated from a patient, if the level of a marker polypeptide is significantly reduced in the sample cells. The term "significantly reduced" refers to a cell phenotype wherein the cell possesses a reduced cellular amount of the marker polypeptide relative to a normal cell of similar tissue origin. For example, a cell may have less than about 50%, 25%, 10%, or 5% of the marker polypeptide compared to that of a normal control cell. In particular, the assay evaluates the level of marker polypeptide in the test cells, and, preferably, compares the measured level with marker polypeptide detected in at least one control-cell, for example, a normal cell and/or a transformed cell of known phenotype.

[160] Of particular importance to the subject invention is the ability to quantitate the level of marker polypeptide as determined by the number of cells associated with a normal or abnormal marker polypeptide level. The number of cells with a particular marker polypeptide phenotype

may then be correlated with patient prognosis. In one embodiment of the invention, the marker polypeptide phenotype of a lesion is determined as a percentage of cells in a biopsy which are found to have abnormally high/low levels of the marker polypeptide. Such expression may be detected by immunohistochemical assays, dot-blot assays, ELISA, and the like.

[161] Where tissue samples are employed, immunohistochemical staining may be used to determine the number of cells having the marker polypeptide phenotype. For such staining, a multiblock of tissue may be taken from the biopsy or other tissue sample and subjected to proteolytic hydrolysis, employing such agents as protease K or pepsin. In certain embodiments, it may be desirable to isolate a nuclear fraction from the sample cells and detect the level of the marker polypeptide in the nuclear fraction.

[162] The tissue samples are fixed by treatment with a reagent such as formalin, glutaraldehyde, methanol, or the like. The samples are then incubated with an antibody (e.g., a monoclonal antibody) with binding specificity for the marker polypeptides. This antibody may be conjugated to a label for subsequent detection of binding. Samples are incubated for a time sufficient for formation of the immunocomplexes. Binding of the antibody is then detected by virtue of a label conjugated to this antibody. Where the antibody is unlabeled, a second labeled antibody may be employed, for example, which is specific for the isotype of the anti-marker polypeptide antibody. Examples of labels which may be employed include radionuclides, fluorescers, chemiluminescers, enzymes, and the like.

[163] Where enzymes are employed, the substrate for the enzyme may be added to the samples to provide a colored or fluorescent product. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase, and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art.

[164] In one embodiment, the assay is performed as a dot blot assay. The dot blot assay finds particular application where tissue samples are employed as it allows determination of the average amount of the marker polypeptide associated with a single cell by correlating the amount of marker polypeptide in a cell-free extract produced from a predetermined number of cells.

[165] It is well established in the cancer literature that tumor cells of the same type (e.g., breast and/or colon tumor cells) may not show uniformly increased expression of individual oncogenes or uniformly decreased expression of individual tumor suppressor genes. There may also be varying levels of expression of a given marker gene even between cells of a given type of cancer, further emphasizing the need for reliance on a battery of tests rather than a single test. Accordingly, in

one aspect, the invention provides for a battery of tests utilizing a number of probes of the invention, in order to improve the reliability and/or accuracy of the diagnostic test.

[166] In one embodiment, the present invention also provides a method wherein nucleic acid probes are immobilized on a DNA chip in an organized array. Oligonucleotides may be bound to a solid support by a variety of processes, including lithography. For example, a chip may hold up to 250,000 oligonucleotides. These nucleic acid probes comprise a nucleotide sequence, for example, at least about 12, 15, 25, or 40 nucleotides in length, and up to all or nearly all of a sequence which is complementary to a portion of the coding sequence of a marker nucleic acid sequence and is differentially expressed in tumor cells. The present invention provides significant advantages over the available tests for various cancers, because it increases the reliability of the test by providing an array of nucleic acid markers on a single chip.

[167] The method includes obtaining a biopsy, which is optionally fractionated by cryostat sectioning to enrich tumor cells to about 80% of the total cell population. The DNA or RNA is then extracted, amplified, and analyzed with a DNA chip to determine the presence or absence of the marker nucleic acid sequences.

[168] In one embodiment, the nucleic acid probes are spotted onto a substrate in a two-dimensional matrix or array. Samples of nucleic acids may be labeled and then hybridized to the probes. Double-stranded nucleic acids, comprising the labeled sample nucleic acids bound to probe nucleic acids, may be detected once the unbound portion of the sample is washed away.

[169] The probe nucleic acids may be spotted on substrates including glass, nitrocellulose, etc. The probes can be bound to the substrate by either covalent bonds or by non-specific interactions, such as hydrophobic interactions. The sample nucleic acids can be labeled using radioactive labels, fluorophores, chromophores, etc.

[170] In yet another embodiment, the invention contemplates using a panel of antibodies which are generated against the marker polypeptides of this invention. Such a panel of antibodies may be used as a reliable diagnostic probe for cancer. The assay of the present invention comprises contacting a biopsy sample containing cells, for example, colon cells, with a panel of antibodies to one or more of the encoded products to determine the presence or absence of the marker polypeptides.

[171] The diagnostic methods of the subject invention may also be employed as follow-up to treatment, for example, quantitation of the level of marker polypeptides may be indicative of the effectiveness of current or previously employed cancer therapies as well as the effect of these therapies upon patient prognosis.

[172] In addition, the marker nucleic acids or marker polypeptides may be utilized as part of a diagnostic panel for initial detection, follow-up screening, detection of reoccurrence, and post-treatment monitoring for chemotherapy or surgical treatment.

[173] Accordingly, the present invention makes available diagnostic assays and reagents for detecting gain and/or loss of marker polypeptides from a cell in order to aid in the diagnosis and phenotyping of proliferative disorders arising from, for example, tumorigenic transformation of cells.

[174] The diagnostic assays described above may be adapted to be used as prognostic assays, as well. Such an application takes advantage of the sensitivity of the assays of the invention to events which take place at characteristic stages in the progression of a tumor. For example, a given marker gene may be up- or down-regulated at a very early stage, perhaps before the cell is irreversibly committed to developing into a malignancy, while another marker gene may be characteristically up- or down-regulated only at a much later stage. Such a method could involve the steps of contacting the mRNA of a test cell with a nucleic acid probe derived from a given marker nucleic acid which is expressed at different characteristic levels in cancerous or precancerous cells at different stages of tumor progression, and determining the approximate amount of hybridization of the probe to the mRNA of the cell, such amount being an indication of the level of expression of the gene in the cell, and thus an indication of the stage of tumor progression of the cell; alternatively, the assay may be carried out with an antibody specific for the gene product of the given marker nucleic acid, contacted with the proteins of the test cell. A battery of such tests will disclose not only the existence and location of a tumor, but also will allow the clinician to select the mode of treatment most appropriate for the tumor, and to predict the likelihood of success of that treatment.

[175] The methods of the invention may also be used to follow the clinical course of a tumor. For example, the assay of the invention may be applied to a tissue sample from a patient; following treatment of the patient for the cancer, another tissue sample is taken and the test repeated. Successful treatment will result in either removal of all cells which demonstrate differential expression characteristic of the cancerous or precancerous cells, or a substantial increase in expression of the gene in those cells, perhaps approaching or even surpassing normal levels.

[176] In yet another embodiment, the invention provides methods for determining whether a subject is at risk for developing a disease, such as a predisposition to develop cancer, associated with aberrant activity of a polypeptide, wherein the aberrant activity of the polypeptide is characterized by detecting the presence or absence of a genetic lesion characterized by at least one of (a) an alteration affecting the integrity of a gene encoding a marker polypeptides, or (b) the mis-expression of the encoding nucleic acid. To illustrate, such genetic lesions may be detected by



ascertaining the existence of at least one of (i) a deletion of one or more nucleotides from the nucleic acid sequence, (ii) an addition of one or more nucleotides to the nucleic acid sequence, (iii) a substitution of one or more nucleotides of the nucleic acid sequence, (iv) a gross chromosomal rearrangement of the nucleic acid sequence, (v) a gross alteration in the level of a messenger RNA transcript of the nucleic acid sequence, (vi) aberrant modification of the nucleic acid sequence, such as of the methylation pattern of the genomic DNA, (vii) the presence of a non-wild type splicing pattern of a messenger RNA transcript of the gene, (viii) a non-wild type level of the marker polypeptide, (ix) allelic loss of the gene, and/or (x) inappropriate post-translational modification of the marker polypeptide.

[177] The present invention provides assay techniques for detecting lesions in the encoding nucleic acid sequence. These methods include, but are not limited to, methods involving sequence analysis, Southern blot hybridization, restriction enzyme site mapping, and methods involving detection of absence of nucleotide pairing between the nucleic acid to be analyzed and a probe.

[178] Specific diseases or disorders, for example, genetic diseases or disorders, are associated with specific allelic variants of polymorphic regions of certain genes, which do not necessarily encode a mutated protein. Thus, the presence of a specific allelic variant of a polymorphic region of a gene in a subject may render the subject susceptible to developing a specific disease or disorder. Polymorphic regions in genes, may be identified, by determining the nucleotide sequence of genes in populations of individuals. If a polymorphic region is identified, then the link with a specific disease may be determined by studying specific populations of individuals, for example, individuals which developed a specific disease, such as cancer. A polymorphic region may be located in any region of a gene, for example, exons, in coding or non-coding regions of exons, introns, and promoter region.

[179] In an exemplary embodiment, there is provided a nucleic acid composition comprising a nucleic acid probe including a region of nucleotide sequence which is capable of hybridizing to a sense or antisense sequence of a gene or naturally occurring mutants thereof, or 5' or 3' flanking sequences or intronic sequences naturally associated with the subject genes or naturally occurring mutants thereof. The nucleic acid of a cell is rendered accessible for hybridization, the probe is contacted with the nucleic acid of the sample, and the hybridization of the probe to the sample nucleic acid is detected. Such techniques may be used to detect lesions or allelic variants at either the genomic or mRNA level, including deletions, substitutions, etc., as well as to determine mRNA transcript levels.

[180] An example of a detection method is allele specific hybridization using probes overlapping the mutation or polymorphic site and having about 5, 10, 20, 25, or 30 nucleotides around the mutation or polymorphic region. In one embodiment of the invention, several probes capable of

hybridizing specifically to allelic variants are attached to a solid phase support, for example, a "chip." Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described, for example, by Cronin, et al., (Human Mutation 7:244, 1996). In one embodiment, a chip may comprise all the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is detected. Accordingly, the identity of numerous allelic variants of one or more genes may be identified in a simple hybridization experiment.

[181] In certain embodiments, detection of the lesion comprises utilizing the probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligase chain reaction (LCR) (*see, e.g.*, Landegran, et al., Science 241:1077-1080, 1988; Nakazaw, et al., Proc. Natl. Acad. Sci. USA 91:360-364, 1994), the latter of which can be particularly useful for detecting point mutations in the gene (*see, e.g.*, Abrahava, et al., Nuc. Acid Res. 23:675-682, 1995). In an illustrative embodiment, the method includes the steps of (i) collecting a sample of cells from a patient, (ii) isolating nucleic acid (*e.g.*, genomic, mRNA, or both) from the cells of the sample, (iii) contacting the nucleic acid sample with one or more primers which specifically hybridize to a nucleic acid sequence under conditions such that hybridization and amplification of the nucleic acid (if present) occurs, and (iv) detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

[182] The invention thus, also encompasses methods of screening for agents which inhibit or enhance the expression of the nucleic acid markers *in vitro*, comprising exposing a cell or tissue in which the marker nucleic acid mRNA is detectable in cultured cells to an agent in order to determine whether the agent is capable of inhibiting or enhancing production of the mRNA; and determining the level of mRNA in the exposed cells or tissue, wherein a decrease in the level of the mRNA after exposure of the cell line to the agent is indicative of inhibition of the marker nucleic acid mRNA production and an increase in mRNA levels is indicative of enhancement of marker mRNA production.

[183] Alternatively, the screening method may include *in vitro* screening of a cell or tissue in which marker protein is detectable in cultured cells to an agent suspected of inhibiting or enhancing production of the marker protein; and determining the level of the marker protein in the cells or tissue, wherein a decrease in the level of marker protein after exposure of the cells or tissue to the agent is indicative of inhibition of marker protein production and an increase on the level of marker protein is indicative of enhancement of marker protein production.

[184] The invention also encompasses *in vivo* methods of screening for agents which inhibit or enhance expression of the marker nucleic acids, comprising exposing a subject having tumor cells in which marker mRNA or protein is detectable to an agent suspected of inhibiting or enhancing production of marker mRNA or protein; and determining the level of marker mRNA or protein in tumor cells of the exposed mammal. A decrease in the level of marker mRNA or protein after exposure of the subject to the agent is indicative of inhibition of marker nucleic acid expression and an increase in the level of marker mRNA or protein is indicative of enhancement of marker nucleic acid expression.

[185] Accordingly, the invention provides a method comprising incubating a cell expressing the marker nucleic acids with a test compound and measuring the mRNA or protein level. The invention further provides a method for quantitatively determining the level of expression of the marker nucleic acids in a cell population, and a method for determining whether an agent is capable of increasing or decreasing the level of expression of the marker nucleic acids in a cell population. The method for determining whether an agent is capable of increasing or decreasing the level of expression of the marker nucleic acids in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating the marker polypeptides from the cell extracts, and (c) quantifying (e.g., in parallel) the amount of an immunocomplex formed between the marker polypeptide and an antibody specific to said polypeptide. The marker polypeptides of this invention may also be quantified by assaying for its bioactivity. Agents that induce an increase in the marker nucleic acid expression may be identified by their ability to increase the amount of immunocomplex formed in the treated cell as compared with the amount of the immunocomplex formed in the control cell. In a similar manner, agents that decrease expression of the marker nucleic acid may be identified by their ability to decrease the amount of the immunocomplex formed in the treated cell extract as compared to the control cell.

#### *Predictive Assays*

[186] Laboratory-based assays, which can predict clinical benefit from a given anti-cancer agent, will greatly enhance the clinical management of patients with cancer. In order to assess this effect, a biomarker associated with the anti-cancer agent may be analyzed in a biological sample (e.g., tumor sample, plasma) before, during, and following treatment.

[187] Another approach to monitor treatment is an evaluation of serum proteomic spectra. Specifically, plasma samples may be subjected to mass spectroscopy (e.g., surface-enhanced laser desorption and ionization) and a proteomic spectra may be generated for each patient. A set of spectra, derived from analysis of plasma from patients before and during treatment, may be analyzed by an iterative searching algorithm, which can identify a proteomic pattern that

completely discriminates the treated samples from the untreated samples. The resulting pattern may then be used to predict the clinical benefit following treatment.

[188] Global gene expression profiling of biological samples (e.g., tumor biopsy samples, blood samples) and bioinformatics-driven pattern identification may be utilized to predict clinical benefit and sensitivity, as well as development of resistance to an anti-cancer agent. For example, RNA isolated from cells derived from whole blood from patients before and during treatment may be used to generate blood cell gene expression profiles utilizing Affymetrix GeneChip technology and algorithms. These gene expression profiles may then predict the clinical benefit from treatment with a particular anti-cancer agent.

[189] Analysis of the biochemical composition of urine by 1D <sup>1</sup>H-NMR (Nuclear Magnetic Resonance) may also be utilized as a predictive assay. Pattern recognition techniques may be used to evaluate the metabolic response to treatment with an anti-cancer agent and to correlate this response with clinical endpoints. The biochemical or endogenous metabolites excreted in urine have been well-characterized by proton NMR for normal subjects (Zuppi, et al., Clin Chim Acta 265:85-97, 1997). These metabolites (approximately 30-40) represent the by-products of the major metabolic pathways, such as the citric acid and urea cycles. Drug-, disease-, and genetic-stimuli have been shown to produce metabolic-specific changes in baseline urine profiles that are indicative of the timeline and magnitude of the metabolic response to the stimuli. These analyses are multi-variant and therefore use pattern recognition techniques to improve data interpretation. Urinary metabolic profiles may be correlated with clinical endpoints to determine the clinical benefit.

#### *Kits*

[190] The invention further provides kits for determining the expression level of genes characteristic of human colon tumor tissue. The kits may be useful for identifying subjects that are predisposed to developing cancer or who have cancer, as well as for identifying and validating therapeutics for cancer. In one embodiment, the kit comprises a computer readable medium on which is stored one or more gene expression profile of diseased cells of cancer, or at least values representing levels of expression of one or more genes characteristic of human colon tumor tissue in a diseased cell. The computer readable medium can also comprise gene expression profiles of counterpart normal cells, diseased cells treated with a drug, and any other gene expression profile described herein. The kit can comprise expression profile analysis software capable of being loaded into the memory of a computer system.

[191] A kit can comprise a microarray comprising probes of genes characteristic of human colon tumor tissue. A kit can comprise one or more probes or primers for detecting the expression level

of one or more genes characteristic of human colon tumor tissue and/or a solid support on which probes attached and which can be used for detecting expression of one or more genes characteristic of human colon tumor tissue in a sample. A kit may further comprise nucleic acid controls, buffers, and instructions for use.

[192] Other kits provide compositions for treating cancer. For example, a kit can also comprise one or more nucleic acids corresponding to one or more genes characteristic of human colon tumor tissue (e.g., for use in treating a patient having cancer). The nucleic acids can be included in a plasmid or a vector (e.g., a viral vector). Other kits comprise a polypeptide encoded by a gene characteristic of cancer or an antibody to a polypeptide. Yet other kits comprise compounds identified herein as agonists or antagonists of genes characteristic of human colon tumor tissue. The compositions may be pharmaceutical compositions comprising a pharmaceutically acceptable excipient.

## EXAMPLES

[193] It will be apparent to those skilled in the art that the examples and embodiments described herein are by way of illustration and not of limitation, and that other examples may be used without departing from the spirit and scope of the present invention, as set forth in the claims.

### *Example 1. Gene Expression Profiling Protocol*

#### *A. Tissue Source*

[194] Human colon tumor tissue and normal adjacent tissue were purchased from the National Disease Research Institute.

#### *B. RNA extraction and cRNA preparation*

[195] Total RNA was extracted from the human tissues using TRIzol reagent (Life Technologies, MD) according to a modified vendor protocol which utilizes the RNeasy protocol (Qiagen, CA). After homogenization with a Brinkmann Polytron PT10/35 (Brinkmann, Switzerland) and phase separation with chloroform, samples were applied to RNeasy columns. RNA samples were treated with DNase I using RNase-free DNase Set (Qiagen, CA).

[196] After elution and quantitation with UV spectrophotometry, each sample was reverse transcribed into double-stranded cDNA using the Gibco Superscript II Choice System for RT-PCR according to vendor protocol (Invitrogen, CA).

[197] Samples were organically extracted and ethanol precipitated. Approximately 1 µg cDNA was then used in an *in vitro* transcription reaction incorporating biotinylated nucleotides using an RNA labeling kit (Enzo Diagnostics, NY). The resulting cRNA was put through RNeasy clean-up protocol and then quantified using UV spectrophotometry. The cRNA (15 µg) was fragmented in the presence of MgOAc and KOAc at 94°C. Fragmented RNA (10 µg) was loaded onto each array, one cRNA sample per array. Arrays were hybridized for 16 hours at 45°C rotating at 60 rpm in an Affymetrix GeneChip Hybridization Oven 640.

#### *C. Microarray Suite 5.0 analysis*

[198] Following hybridization, arrays were stained with Phycoerythrin-conjugated Streptavidin, placed in an Agilent GeneArray Scanner and then exposed to a 488 nm laser, causing excitation of the phycoerythrin. The Microarray Suite 5.0 software digitally converts the intensity of light given off by the array into a numeric value indicative of levels of gene expression. Because each array represents a single sample, tumor RNA was compared to the RNA isolated from normal adjacent tissue.

*D. Spotfire analysis*

[199] The purpose of this analysis is to generate sets of markers to distinguish between colon cancer and normal tissues (nucleic acid sequences SEQ ID NOs. 1-96 and corresponding amino acid sequences SEQ ID NOs. 97-191). Marker Set One (Table 1) represents the probe set which shows the most "distinct" expression levels among cancer and normal tissues. This marker set was derived using the following method:

1. The data was imported into Spotfire DecisionSite for Functional Genomics v. 7.1 (Spotfire, Inc., Somerville, MA).
2. The 10 pairs of samples were grouped into cancer and normal.
3. A Treatment Comparison was performed using the Distinction Calculation option.

[200] The probe sets which had a Distinction value of greater than or equal to 1.5 (up-regulated in cancer) or less than or equal to -1.5 (down-regulated in cancer) were selected and are shown in Table 1.

[201] Marker Set Two (Table 2) represents a set of probe sets that is an optimum set for the prediction of whether or not a tissue is cancerous using a support vector machine. The optimal set is determined to be the one that shows the greatest prediction accuracy with the least error. This marker set was derived using the following method:

1. The data was imported into Spotfire.
2. A Treatment Comparison between cancer and normal tissues was performed using the t-test option.
3. The following criteria were used to select the probe sets:
  - a. The data showed that the probe sets were all "Present," as determined by the Affymetrix Microarray Suite software v. 5.0 (Affymetrix, Inc., Santa Clara, CA).
  - b. The data for the probe set showed a p-value of less than or equal to 0.001 according to the t-test.
4. All probe sets not meeting these criteria were eliminated from further analysis.
5. The remaining data were used in a selection process using custom software in conjunction with a modified version of the svm-train program (C++ version) which is part of LIBSVM (Chang and Lin, LIBSVM: A Library for Support Vector Machines, 2001. Software available from <http://www.csie.ntu.edu.tw/~cjlin/libsvm>). The custom software was written in the Perl language v. 5.004. The software was run on an SGI Origin 2000 running the IRIX 6.5.7f operation system. This software was used in the following manner:

- a. The Perl program was used as a "wrapper" to control svm-train. Its functions were to select subsets of the data and feed these sets to svm-train for training support vector machines (SVM).
- b. Training consisted of many elimination rounds. During each round many support vector machines were trained using ten fold cross validation in order to estimate accuracy and error. Each SVM was trained on all data except that the data from one probe set was left out. One probe set was eliminated from the data set at each round. This was the probe set that showed the best error and/or accuracy for the SVM when it was eliminated.
- c. Training continued until there was only one probe set left.
- d. The set of probe sets that showed the greatest accuracy with the least error was selected and is shown in Table 2.

The input arguments to svm-train were `-s 0 -t 0 -c 1 -v 10`

[202] Marker Set Three (Table 3) represents a set of probe sets that is an optimum set for the prediction of whether or not a tissue is cancerous using a support vector machine. The optimal set is determined to be the one that shows the greatest prediction accuracy with the least error. This marker set was derived using the method described for Marker Set 2 with the following exceptions:

1. The data set was not limited to those probe sets that showed a t-test p-value of less than or equal to 0.001.

[203] Five percent of the probe sets were eliminated at each round until 100 probe sets remained. Then, only one probe set was eliminated during each round.



Table 1. Colon Tumor Marker (Set One)

SEQ ID NO	Probe Set	Gene Symbol	Title	Genbank Accession	Unigene Cluster	Distinction - Cancer
2	200037_s_at	CBX3	chromobox homolog 3 (HP1 gamma homolog, Drosophila)	NM_016587.1	Hs.278554	2.12
5	200687_s_at	SF3B3	splicing factor 3b, subunit 3, 130kDa	NM_012426.1	Hs.195614	1.54
6	200696_s_at	GSN	gelsolin (amyloidosis, Finnish type)	NM_000177.1	Hs.290970	-1.63
7	200884_at	CKB	creatine kinase, brain	NM_001823.1	Hs.173724	-1.57
10	201091_s_at	CBX3	chromobox homolog 3 (HP1 gamma homolog, Drosophila)	BE748755	Hs.278554	1.61
13	201497_x_at	MYH11	myosin, heavy polypeptide 11, smooth muscle	NM_022844.1	Hs.78344	-1.72
16	202125_s_at	ALS2CR3	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 3	NM_015049.1	Hs.154248	-1.76
21	202350_s_at	MATN2	matrilin 2	NM_002380.2	Hs.19368	-1.81
25	202894_at	EPHB4	EphB4	NM_004444.1	Hs.155227	1.64
27	203213_at	CDC2	cell division cycle 2, G1 to S and G2 to M	AL524035	Hs.334562	1.51
29	203462_x_at	EIF3S9	eukaryotic translation initiation factor 3, subunit 9 eta, 116kDa	NM_003751.1	Hs.57783	1.57
30	203498_at	DSCR1L1	Down syndrome critical region gene 1-like 1	NM_005822.1	Hs.156007	-1.81
31	203510_at	MET	met proto-oncogene (hepatocyte growth factor receptor)	BG170541	Hs.285754	1.7
32	203680_at	PRKAR2B	protein kinase, cAMP-dependent, regulatory, type II, beta	NM_002736.1	Hs.77439	-1.65
34	204036_at	EDG2	endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	AW269335	Hs.75794	-1.91
35	204170_s_at	CKS2	CDC28 protein kinase 2	NM_001827.1	Hs.83758	1.64
38	204529_s_at	TOX	thymus high mobility group box protein TOX	AI961231	Hs.184297	-1.5
40	204719_at	ABCA8	ATP-binding cassette, sub-family A (ABCI), member 8	NM_007168.1	Hs.38095	-1.59
41	204773_at	IL11RA	interleukin 11 receptor, alpha	NM_004512.1	Hs.64310	-1.56
43	205032_at	ITGA2	integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)	NM_002203.2	Hs.271986	1.6
46	205498_at	GHR	growth hormone receptor	NM_000163.1	Hs.125180	-1.58
48	206306_at	RYR3	ryanodine receptor 3	NM_001036.1	Hs.93499	-1.71

49	206364_at	KIF14	kinesin family member 14	NM_014875.1	Hs.3104	2.19
50	206910_x_at	HFL3	H factor (complement)-like 3	NM_005666.1	Hs.154224	-1.8
51	207761_s_at	DKFZF586A0522	DKFZF586A0522 protein	NM_014033.1	Hs.288771	-1.74
55	208688_x_at	EIF3S9	eukaryotic translation initiation factor 3, subunit 9 eta, 116kDa	U78525.1	Hs.57783	1.51
61	210946_at	PPAP2A	phosphatidic acid phosphatase type 2A	AF014403.1	Hs.41569	-1.66
62	211501_s_at	EIF3S9	eukaryotic translation initiation factor 3, subunit 9 eta, 116kDa	BC001173.1	Hs.57783	1.85
63	211747_s_at	LSM5	U6 snRNA-associated Sm-like protein	BC005938.1	Hs.227280	1.61
64	211998_at	H3F3B	H3 histone, family 3B (H3.3B)	NM_005324.1	Hs.180877	-1.54
67	212378_at	GART	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminimidazole synthetase	BE966876	Hs.82285	1.65
68	212510_at	KIAA0089	KIAA0089 protein	AA135522	Hs.82432	-1.68
70	213131_at	OLFMI	olfactomedin 1	R38389	Hs.74376	-1.71
72	213436_at	CNR1	cannabinoid receptor 1 (brain)	U73304	Hs.75110	-1.73
73	213438_at		Homo sapiens cDNA FLJ34019 fs, clone FCBBF2002898	AA995925	Hs.7309	-1.83
74	213451_x_at	TNXB	tenascin XB	BE044614	Hs.169886	-1.74
75	213658_at		Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 26539	BE858194	Hs.323053	-1.54
79	218332_at	BEX1	brain expressed, X-linked 1	NM_018476.1	Hs.334370	-1.58
82	218594_at	FLJ10359	hypothetical protein FLJ10359	NM_018072.1	Hs.285861	1.68
86	218984_at	FLJ20485	hypothetical protein FLJ20485	NM_019042.1	Hs.98806	1.87
87	219293_s_at	PTD004	hypothetical protein PTD004	NM_013341.1	Hs.86347	1.76
88	219647_at	POP2	popeye protein 2	NM_022135.1	Hs.77208	-1.93
89	219787_s_at	ECT2	epithelial cell transforming sequence 2 oncogene	NM_018098.1	Hs.122579	2.27
91	220591_s_at	FLJ22843	hypothetical protein FLJ22843	NM_025184.1	Hs.301143	-1.52
92	221016_s_at	TCF-3	HMG-box transcription factor TCF-3	NM_031283.1	Hs.102367	-1.52
95	222043_at	CLU	clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)	AI982754	Hs.75106	-1.57
96	41037_at	TEAD4	TEA domain family member 4	U63824	Hs.94865	1.77

Table 2. Colon Tumor Marker (Set Two)

SEQ ID NO	Probe Set	Gene Symbol	Title	Genbank Accession	Unigene Cluster
1	200002_at	RPL35	ribosomal protein L35	NM_007209.1	Hs.182825
3	200096_s_at	ATP6V0E	ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e	AI862255	Hs.24322
4	200652_at	SSR2	signal sequence receptor, beta (translocon-associated protein beta)	NM_003145.2	Hs.74564
6	200696_s_at	GSN	gelsolin (amyloidosis, Finnish type)	NM_000177.1	Hs.290070
10	201091_s_at	CBX3	chromobox homolog 3 (HP1 gamma homolog, Drosophila)	BE748755	Hs.278554
14	201527_at	ATP6V1F	ATPase, H+ transporting, lysosomal 14kDa, V1 subunit F	NM_004231.1	Hs.78089
17	202244_at	PSMB4	proteasome (prosome, macropain) subunit, beta type, 4	NM_002796.1	Hs.89545
18	202311_s_at	COL1A1	collagen, type I, alpha 1	NM_000088.1	Hs.172928
19	202325_s_at	ATP5J	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit F6	NM_001685.1	Hs.73851
21	202350_s_at	MATN2	matrilin 2	NM_002380.2	Hs.19368
23	202404_s_at	COL1A2	collagen, type I, alpha 2	NM_000089.1	Hs.179573
24	202741_at	PRKACB	protein kinase, cAMP-dependent, catalytic, beta	AA130247	Hs.87773
26	202998_s_at	LOXL2	lysyl oxidase-like 2	NM_002318.1	Hs.83354
28	203380_x_at	SFRS5	splicing factor, arginine/serine-rich 5	NM_006925.1	Hs.166975
31	203510_at	MET	met proto-oncogene (hepatocyte growth factor receptor)	BG170541	Hs.285754
33	203989_x_at	F2R	coagulation factor II (thrombin) receptor	NM_001992.2	Hs.128087
36	204244_s_at	ASK	activator of S phase kinase	NM_006716.1	Hs.152759
37	204294_at	AMT	aminomethyltransferase (glycine cleavage system protein T)	NM_000481.1	Hs.102

44	205110_s_at	FGF13	fibroblast growth factor 13	NM_004114.1	Hs.6540
45	205200_at	TNA	tetranectin (plasminogen binding protein)	NM_003278.1	Hs.65424
46	205498_at	GHR	growth hormone receptor	NM_000163.1	Hs.125180
47	205499_at	SRPUL	sushi-repeat protein	NM_014467.1	Hs.126782
49	206364_at	KIF14	kinesin family member 14	NM_014875.1	Hs.3104
52	208308_s_at	GPI	glucose phosphate isomerase	NM_000175.1	Hs.279789
53	208394_x_at	ESM1	endothelial cell-specific molecule 1	NM_007036.2	Hs.41716
56	208694_at	PRKDC	protein kinase, DNA-activated, catalytic polypeptide	U47077.5	Hs.155637
59	210513_s_at	VEGF	vascular endothelial growth factor	AF091352.1	Hs.73793
60	210776_x_at	TCF3	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	M31222.1	Hs.101047
63	211747_s_at	LSM5	U6 snRNA-associated Sm-like protein	BC005938.1	Hs.227280
65	212111_at	STX12	syntaxin 12	AL035306.1	Hs.106823
66	212116_at	RFP	ret finger protein	NM_006510.1	Hs.142653
69	213049_at		Homo sapiens mRNA; cDNA DKFZp667F074 (from clone DKFZp667F074)	BG436400	Hs.378933
76	214636_x_at	MYO1C	myosin IC	BE790157	Hs.286226
77	214988_s_at	SON	SON DNA binding protein	X63071.1	Hs.92909
81	218547_at	FLJ13102	hypothetical protein FLJ13102	NM_024887.1	Hs.225160
90	219918_s_at	FLJ10517	hypothetical protein FLJ10517	NM_018123.1	Hs.121028

Table 3. Colon Tumor Marker (Set Three)

SEQ ID NO	Probe Set	Gene Symbol	Title	Genbank Accession	Unigene Cluster
8	200900_s_at	M6PR	mannose-6-phosphate receptor (cation dependent)	AI583537	Hs.75709
9	201001_s_at	UBE2V1	ubiquitin-conjugating enzyme E2 variant 1	BG164064	Hs.75875
11	201206_s_at	RRBP1	ribosome binding protein 1 homolog 180kDa (dog)	NM_004587.1	Hs.98614
12	201232_s_at	PSMD13	proteasome (prosome, macropain) 26S subunit, non-ATPase, 13	NM_002817.1	Hs.279554
15	201563_at	SORD	sorbitol dehydrogenase	L29008.1	Hs.878
20	202326_at	BAT8	HLA-B associated transcript 8	NM_006709.1	Hs.75196
22	202370_s_at	CBFB	core-binding factor, beta subunit	NM_001755.1	Hs.179881
39	204537_s_at	GABRE	gamma-aminobutyric acid (GABA) A receptor, epsilon	NM_004961.2	Hs.22785
42	204793_at	KIAA0443	KIAA0443 gene product	NM_014710.1	Hs.113082
44	205110_s_at	FGF13	fibroblast growth factor 13	NM_004114.1	Hs.6540
54	208680_at	PRDX1	peroxiredoxin 1	L19184.1	Hs.180909
57	208712_at	CCND1	cyclin D1 (PRAD1; parathyroid adenomatosis 1)	M73554.1	Hs.82932
58	208713_at	E1B-AP5	E1B-55kDa-associated protein 5	BF724216	Hs.155218
59	210513_s_at	VEGF	vascular endothelial growth factor	AF091352.1	Hs.73793
71	213275_x_at	CTSB	cathepsin B	BE875786	Hs.297939
78	218053_at	FBNP3	formin binding protein 3	NM_017892.1	Hs.107213
80	218518_at	C5orf5	chromosome 5 open reading frame 5	NM_016603.1	Hs.82035
83	218677_at	LOC57402	S100-type calcium binding protein A14	NM_020672.1	Hs.288998
84	218882_s_at	WDR3	WD repeat domain 3	NM_006784.1	Hs.33085
85	218982_s_at	MRPS17	mitochondrial ribosomal protein S17	NM_015969.1	Hs.44298
93	221667_s_at	H11	protein kinase H11	AF133207.1	Hs.111676
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We claim:

1. A method for providing a patient diagnosis for colon cancer, comprising the steps of:
  - (a) determining the level of expression of one or more genes or gene products in a first biological sample taken from the patient;
  - (b) determining the level of expression of one or more genes or gene products in at least a second biological sample taken from a normal patient sample; and
  - (c) comparing the level of expression of one or more genes or gene products in the first biological sample with the level of expression of one or more genes or gene products in the second biological sample;

wherein a change in the level of expression of one or more genes or gene products in the first biological sample compared to the level of expression of one or more genes or gene products in the second biological sample is a diagnostic of the disease.
2. The method of claim 1, wherein one or more genes are selected from the group consisting of SEQ ID NOs: 1-96.
3. The method of claim 1, wherein one or more gene products are polypeptides selected from the group consisting of SEQ ID NOs: 97-191.
4. A method for distinguishing between normal and disease tissues, comprising the steps of:
  - (a) determining the level of expression of one or more genes or gene products in a first biological sample of a disease tissue;
  - (b) determining the level of expression of one or more genes or gene products in at least a second biological sample taken from normal tissue; and
  - (c) comparing the level of expression of one or more genes or gene products in the first biological sample with the level of expression of one or more genes or gene products in the second biological sample;

wherein a change in the level of expression of one or more genes or gene products in the first biological sample compared to the level of expression of one or more genes or gene products in the second biological sample is indicative of a disease state.
5. The method of claim 4, wherein one or more genes are selected from the group consisting of SEQ ID NOs: 1-96.

6. The method of claim 4, wherein one or more gene products are polypeptides selected from the group consisting of SEQ ID NOs: 97-191.
7. A method to monitor the response of a patient being treated for colon cancer by administering a anti-cancer agent, comprising the steps of:
  - (a) determining the level of expression of one or more genes or gene products in a first biological sample taken from the patient prior to treatment with the anti-cancer agent;
  - (b) determining the level of expression of one or more genes or gene products in at least a second biological sample taken from the patient subsequent to the treatment with the anti-cancer agent; and
  - (c) comparing the level of expression of one or more one genes(s) or gene products in the second biological sample with the level of expression of one or more one genes(s) or gene products in the first biological sample;wherein a change in the level of expression of one or more genes or gene products in the second biological sample compared to the level of expression of one or more genes or gene products in the first biological sample indicates the efficacy of the treatment with the anti-cancer agent.
8. The method of claim 7, wherein one or more genes are selected from the group consisting of SEQ ID NOs: 1-96.
9. The method of claim 7, wherein one or more gene products are polypeptides selected from the group consisting of SEQ ID NOs: 97-191.
10. A method for identifying a compound useful for the treatment of colon cancer comprising the steps of:
  - (a) analyzing the level of expression of one or more genes and/or gene products in a cell or tissue sample prior to treatment with the compound;
  - (b) analyzing the level of expression of one or more genes and/or gene products in a cell or tissue sample subsequent to treatment with the compound;wherein a variation in the expression level of the gene and/or gene product is indicative of drug efficacy.
11. The method of claim 10, wherein one or more genes are selected from the group consisting of SEQ ID NOs: 1-96.

12. The method of claim 10, wherein one or more gene products are polypeptides selected from the group consisting of SEQ ID NOs: 97-191.
13. An array for distinguishing between normal and disease tissues, comprising two or more probes corresponding to two or more genes selected from the group consisting of SEQ ID NOs: 1-96.
14. An array for distinguishing between normal and disease tissues, comprising two or more polypeptides selected from the group consisting of SEQ ID NOs: 97-191.



## SEQUENCE LISTING

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 Taylor, Ian

<120> EXPRESSION PROFILES FOR COLON CANCER AND METHODS OF USE

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 <211> 1662  
 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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atgatcagt tgaatcccag tggcgtaatc caagatttta ttttttttg tgatgccgtt	300
gcatcatgga ttaacccaaa agatgatctc agagacatgt tctgtaagat ccttcatgga	360
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gttacccttt acagggggga agggtaaacc agtagggaat acagtacaat cccaacccta	600
ctgggagggg cgggaggag gtgttgccgt cactgtatta agtcgatgtt gggaaacgtt	660
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ggaacaattc tatagcgac aataaaggaa acctaagaat ngnagtnnnn aatagtaaag	900
aagctttttt ttttttttaa tttaaagttt ttttatgtaa gttttccac atgangngnn	960
nnngnttngc atgtngatga agaactacac aaagaaaact aatatagtta aaagtcagct	1020
ngccttcng tagtagaagc aggttctngg aagttacaat ttaaggtacc caaaaaagt	1080
nggaaataaa acaaaacaaa cataaacaat gaagcaccct gntgaaatgc caaatgagtc	1140
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caactaaag atgacatctt aattttgcat tgaacattaa tgtagcggat ataatttgat	1260
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aatgtgaaa gctgatatac ctgtgcaaaa tctttgcctc tgtgctgtca gtgtgatgtg	1680
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agttgaaaa tgattgctat atttcaatgt ttattccac tcaacatact gccttctaag	1860
cttccctttt ttgttcaaa gcatgatctt aaagatatgt ttaagttaat ggatgtaatg	1920
cagggttcct acactgtatt ttggcgcatg ttggtggccc tctgtgccct agatatatgc	1980
acacaggggt caagttaaaa gctacagagt gaaagttggg ttggatcctc ttcatttcat	2040

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cctaactggg acacttgatc ttgtgttcac atgaaagtgc aagtccttat taatttggat 2220
tgcctgaaca gtgtatccca tgatgatgaa ggaaaatgga gagatttttc tttttaactc 2280
tgctggtcag agatgaagcc acgcctttcc atttttcaat gctgcatatt taatctgcaa 2340
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accgcaaaaa gcaccgggag gagtgagatg tggatgttgc ttttgacact acgggggcat 180
ctgagtccag ctccccccaa gatgagctgc agccccccag agagagctct gcacgtcacc 240
aagtaaccag gccccagcct ccaggcccc aactccgccc agcctctccc cgctctggat 300
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<212> DNA  
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gcaccttggg accggtccaa cgagcgtcc tccaagcggg gccttgagg gcacggccgg      180
caccattacc tccaacgagt ggagctctcc cacctcccct gaggggagca ccgcctctgg      240
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tattgagcag agtttccagg aggccctcgc catctaccgc ccctgtggca ggcgcaaaat      360
catcctgtcg gacgagggca agatgtatgg tcgaaacgag ctgattgccc gctacatcaa      420
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cctgcagagc atggctgcca tgtcgtctgc acagatcatc tccgccacgg ccttcacag      600
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tttgccaggc caagccgaaa cgtcccatga tgtgaagcct ttctctcagc aaacctatgc      720
tgtccagcct ccgctgcctc tgccagggtt tgagtctcct gcaggggccg ccccatcgcc      780
ctctgcgccc ccggcacccc catggcaggg ccgcaggcgt ggagctcca agctctggat      840
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gttcgtgcac attggccagt ccagcccaag ctacctgcgc ccctacctcg aagccgtgga      960
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caagagagct gagaggagca gttgtgactc taccaggaa caaactgtgc ctgaacctga      1620
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<212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 97

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Leu Lys Gln Leu Asp Asp Leu Lys Val Glu Leu Ser Gln Leu Arg Val  
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Ala Lys Val Thr Gly Gly Ala Ala Ser Lys Leu Ser Lys Ile Arg Val  
 35 40 45

Val Arg Lys Ser Ile Ala Arg Val Leu Thr Val Ile Asn Gln Thr Gln  
 50 55 60

Lys Glu Asn Leu Arg Lys Phe Tyr Lys Gly Lys Lys Tyr Lys Pro Leu  
 65 70 75 80

Asp Leu Arg Pro Lys Lys Thr Arg Ala Met Arg Arg Arg Leu Asn Lys  
 85 90 95

His Glu Glu Asn Leu Lys Thr Lys Lys Gln Gln Arg Lys Glu Arg Leu  
 100 105 110

Tyr Pro Leu Arg Lys Tyr Ala Val Lys Ala  
 115 120

&lt;210&gt; 98

&lt;211&gt; 183

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

Met Ala Ser Asn Lys Thr Thr Leu Gln Lys Met Gly Lys Lys Gln Asn  
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Gly Lys Ser Lys Lys Val Glu Glu Ala Glu Pro Glu Glu Phe Val Val  
 20 25 30

Glu Lys Val Leu Asp Arg Arg Val Val Asn Gly Lys Val Glu Tyr Phe  
 35 40 45

Leu Lys Trp Lys Gly Phe Thr Asp Ala Asp Asn Thr Trp Glu Pro Glu  
 50 55 60

Glu Asn Leu Asp Cys Pro Glu Leu Ile Glu Ala Phe Leu Asn Ser Gln  
 65 70 75 80

Lys Ala Gly Lys Glu Lys Asp Gly Thr Lys Ser Leu Ser Asp  
 85 90

85                                      90                                      95  
 Ser Glu Ser Asp Asp Ser Lys Ser Lys Lys Lys Arg Asp Ala Ala Asp  
    100                                      105                                      110  
 Lys Pro Arg Gly Phe Ala Arg Gly Leu Asp Pro Glu Arg Ile Ile Gly  
    115                                      120                                      125  
 Ala Ile Asp Ser Ser Gly Glu Leu Met Phe Leu Met Lys Trp Lys Asp  
    130                                      135                                      140  
 Ser Asp Glu Ala Asp Leu Val Leu Ala Lys Glu Ala Asn Met Lys Cys  
    145                                      150                                      155                                      160  
 Pro Gln Ile Val Ile Ala Phe Tyr Glu Glu Arg Leu Thr Trp His Ser  
    165                                      170                                      175  
 Cys Pro Glu Asp Glu Ala Gln  
    180

<210> 99  
 <211> 80  
 <212> PRT  
 <213> Homo sapiens

<400> 99

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 Gly Phe Val Gly Phe Leu Val Pro Trp Phe Ile Pro Lys Gly Pro Asn  
    20                                      25                                      30  
 Arg Gly Val Ile Ile Thr Met Leu Val Thr Cys Ser Val Cys Cys Tyr  
    35                                      40                                      45  
 Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu Asn Pro Leu Phe Gly  
    50                                      55                                      60  
 Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr Leu Lys Tyr His Trp Pro  
 65                                      70                                      75                                      80

<210> 100  
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 <212> PRT  
 <213> Homo sapiens

<400> 100

Met Arg Leu Leu Ser Phe Val Val Leu Ala Leu Phe Ala Val Thr Gln  
 1                                      5                                      10                                      15



Ala Glu Glu Gly Ala Arg Leu Leu Ala Ser Lys Ser Leu Leu Asn Arg  
20 25 30

Tyr Ala Val Glu Gly Arg Asp Leu Thr Leu Gln Tyr Asn Ile Tyr Asn  
35 40 45

Val Gly Ser Ser Ala Ala Leu Asp Val Glu Leu Ser Asp Asp Ser Phe  
50 55 60

Pro Pro Glu Asp Phe Gly Ile Val Ser Gly Met Leu Asn Val Lys Trp  
65 70 75 80

Asp Arg Ile Ala Pro Ala Ser Asn Val Ser His Thr Val Val Leu Arg  
85 90 95

Pro Leu Lys Ala Gly Tyr Phe Asn Phe Thr Ser Ala Thr Ile Thr Tyr  
100 105 110

Leu Ala Gln Glu Asp Gly Pro Val Val Ile Gly Ser Thr Ser Ala Pro  
115 120 125

Gly Gln Gly Gly Ile Leu Ala Gln Arg Glu Phe Asp Arg Arg Phe Ser  
130 135 140

Pro His Phe Leu Asp Trp Ala Ala Phe Gly Val Met Thr Leu Pro Ser  
145 150 155 160

Ile Gly Ile Pro Leu Leu Leu Trp Tyr Ser Ser Lys Arg Lys Tyr Asp  
165 170 175

Thr Pro Lys Thr Lys Lys Asn  
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<400> 101

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Ala Ile His Gly Asn Phe Ser Gly Thr Lys Gln Gln Glu Ile Val Val  
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Ser Arg Gly Lys Ile Leu Glu Leu Leu Arg Pro Asp Pro Asn Thr Gly  
35 40 45

Lys Val His Thr Leu Leu Thr Val Glu Val Phe Gly Val Ile Arg Ser  
 50 55 60  
 Leu Met Ala Phe Arg Leu Thr Gly Gly Thr Lys Asp Tyr Ile Val Val  
 65 70 75 80  
 Gly Ser Asp Ser Gly Arg Ile Val Ile Leu Glu Tyr Gln Pro Ser Lys  
 85 90 95  
 Asn Met Phe Glu Lys Ile His Gln Glu Thr Phe Gly Lys Ser Gly Cys  
 100 105 110  
 Arg Arg Ile Val Pro Gly Gln Phe Leu Ala Val Asp Pro Lys Gly Arg  
 115 120 125  
 Ala Val Met Ile Ser Ala Ile Glu Lys Gln Lys Leu Val Tyr Ile Leu  
 130 135 140  
 Asn Arg Asp Ala Ala Ala Arg Leu Thr Ile Ser Ser Pro Leu Glu Ala  
 145 150 155 160  
 His Lys Ala Asn Thr Leu Val Tyr His Val Val Gly Val Asp Val Gly  
 165 170 175  
 Phe Glu Asn Pro Met Phe Ala Cys Leu Glu Met Asp Tyr Glu Glu Ala  
 180 185 190  
 Gly Asn Asp Pro Thr Gly Glu Ala Ala Ala Asn Thr Gln Gln Thr Leu  
 195 200 205  
 Thr Phe Tyr Glu Leu Asp Leu Gly Leu Asn His Val Val Arg Lys Tyr  
 210 215 220  
 Ser Glu Pro Leu Glu Glu His Gly Asn Phe Leu Ile Thr Val Pro Gly  
 225 230 235 240  
 Gly Ser Asp Gly Pro Ser Gly Val Leu Ile Cys Ser Glu Asn Tyr Ile  
 245 250 255  
 Thr Tyr Lys Asn Phe Gly Asp Gln Pro Asp Ile Arg Cys Pro Ile Pro  
 260 265 270  
 Arg Arg Arg Asn Asp Leu Asp Asp Pro Glu Arg Gly Met Ile Phe Val  
 275 280 285  
 Cys Ser Ala Thr His Lys Thr Lys Ser Met Phe Phe Phe Trp Ala Gln  
 290 295 300

Thr Glu Gln Gly Asp Ile Phe Lys Ile Thr Leu Glu Thr Asp Glu Asp  
 305 310 315 320  
 Met Val Thr Glu Ile Arg Leu Lys Tyr Phe Asp Thr Val Pro Val Ala  
 325 330 335  
 Ala Ala Met Cys Val Leu Lys Thr Gly Phe Leu Phe Val Ala Ser Glu  
 340 345 350  
 Phe Gly Asn His Tyr Leu Tyr Gln Ile Ala His Leu Gly Asp Asp Asp  
 355 360 365  
 Glu Glu Pro Glu Phe Ser Ser Ala Met Pro Leu Glu Glu Gly Asp Thr  
 370 375 380  
 Phe Phe Phe Gln Pro Arg Pro Leu Lys Asn Leu Val Leu Val Asp Glu  
 385 390 395 400  
 Leu Asp Ser Leu Ser Pro Ile Leu Phe Cys Gln Ile Ala Asp Leu Ala  
 405 410 415  
 Asn Glu Asp Thr Pro Gln Leu Tyr Val Ala Cys Gly Arg Gly Pro Arg  
 420 425 430  
 Ser Ser Leu Arg Val Leu Arg His Gly Leu Glu Val Ser Glu Met Ala  
 435 440 445  
 Val Ser Glu Leu Pro Gly Asn Pro Asn Ala Val Trp Thr Val Arg Arg  
 450 455 460  
 His Ile Glu Asp Glu Phe Asp Ala Tyr Ile Ile Val Ser Phe Val Asn  
 465 470 475 480  
 Ala Thr Leu Val Leu Ser Ile Gly Glu Thr Val Glu Glu Val Thr Asp  
 485 490 495  
 Ser Gly Phe Leu Gly Thr Thr Pro Thr Leu Ser Cys Ser Leu Leu Gly  
 500 505 510  
 Asp Asp Ala Leu Val Gln Val Tyr Pro Asp Gly Ile Arg His Ile Arg  
 515 520 525  
 Ala Asp Lys Arg Val Asn Glu Trp Lys Thr Pro Gly Lys Lys Thr Ile  
 530 535 540  
 Val Lys Cys Ala Val Asn Gln Arg Gln Val Val Ile Ala Leu Thr Gly  
 545 550 555 560

Gly Glu Leu Val Tyr Phe Glu Met Asp Pro Ser Gly Gln Leu Asn Glu  
565 570 575

Tyr Thr Glu Arg Lys Glu Met Ser Ala Asp Val Val Cys Met Ser Leu  
580 585 590

Ala Asn Val Pro Pro Gly Glu Gln Arg Ser Arg Phe Leu Ala Val Gly  
595 600 605

Leu Val Asp Asn Thr Val Arg Ile Ile Ser Leu Asp Pro Ser Asp Cys  
610 615 620

Leu Gln Pro Leu Ser Met Gln Ala Leu Pro Ala Gln Pro Glu Ser Leu  
625 630 635 640

Cys Ile Val Glu Met Gly Gly Thr Glu Lys Gln Asp Glu Leu Gly Glu  
645 650 655

Arg Gly Ser Ile Gly Phe Leu Tyr Leu Asn Ile Gly Leu Gln Asn Gly  
660 665 670

Val Leu Leu Arg Thr Val Leu Asp Pro Val Thr Gly Asp Leu Ser Asp  
675 680 685

Thr Arg Thr Arg Tyr Leu Gly Ser Arg Pro Val Lys Leu Phe Arg Val  
690 695 700

Arg Met Gln Gly Gln Glu Ala Val Leu Ala Met Ser Ser Arg Ser Trp  
705 710 715 720

Leu Ser Tyr Ser Tyr Gln Ser Arg Phe His Leu Thr Pro Leu Ser Tyr  
725 730 735

Glu Thr Leu Glu Phe Ala Ser Gly Phe Ala Ser Glu Gln Cys Pro Glu  
740 745 750

Gly Ile Val Ala Ile Ser Thr Asn Thr Leu Arg Ile Leu Ala Leu Glu  
755 760 765

Lys Leu Gly Ala Val Phe Asn Gln Val Ala Phe Pro Leu Gln Tyr Thr  
770 775 780

Pro Arg Lys Phe Val Ile His Pro Glu Ser Asn Asn Leu Ile Ile Ile  
785 790 795 800

Glu Thr Asp His Asn Ala Tyr Thr Glu Ala Thr Lys Ala Gln Arg Lys  
805 810 815

Gln Gln Met Ala Glu Glu Met Val Glu Ala Ala Gly Glu Asp Glu Arg  
 820 825 830  
 Glu Leu Ala Ala Glu Met Ala Ala Ala Phe Leu Asn Glu Asn Leu Pro  
 835 840 845  
 Glu Ser Ile Phe Gly Ala Pro Lys Ala Gly Asn Gly Gln Trp Ala Ser  
 850 855 860  
 Val Ile Arg Val Met Asn Pro Ile Gln Gly Asn Thr Leu Asp Leu Val  
 865 870 875 880  
 Gln Leu Glu Gln Asn Glu Ala Ala Phe Ser Val Ala Val Cys Arg Phe  
 885 890 895  
 Ser Asn Thr Gly Glu Asp Trp Tyr Val Leu Val Gly Val Ala Lys Asp  
 900 905 910  
 Leu Ile Leu Asn Pro Arg Ser Val Ala Gly Gly Phe Val Tyr Thr Tyr  
 915 920 925  
 Lys Leu Val Asn Asn Gly Glu Lys Leu Glu Phe Leu His Lys Thr Pro  
 930 935 940  
 Val Glu Glu Val Pro Ala Ala Ile Ala Pro Phe Gln Gly Arg Val Leu  
 945 950 955 960  
 Ile Gly Val Gly Lys Leu Leu Arg Val Tyr Asp Leu Gly Lys Lys Lys  
 965 970 975  
 Leu Leu Arg Lys Cys Glu Asn Lys His Ile Ala Asn Tyr Ile Ser Gly  
 980 985 990  
 Ile Gln Thr Ile Gly His Arg Val Ile Val Ser Asp Val Gln Glu Ser  
 995 1000 1005  
 Phe Ile Trp Val Arg Tyr Lys Arg Asn Glu Asn Gln Leu Ile Ile  
 1010 1015 1020  
 Phe Ala Asp Asp Thr Tyr Pro Arg Trp Val Thr Thr Ala Ser Leu  
 1025 1030 1035  
 Leu Asp Tyr Asp Thr Val Ala Gly Ala Asp Lys Phe Gly Asn Ile  
 1040 1045 1050  
 Cys Val Val Arg Leu Pro Pro Asn Thr Asn Asp Glu Val Asp Glu  
 1055 1060 1065

Asp Pro Thr Gly Asn Lys Ala Leu Trp Asp Arg Gly Leu Leu Asn  
 1070 1075 1080  
 Gly Ala Ser Gln Lys Ala Glu Val Ile Met Asn Tyr His Val Gly  
 1085 1090 1095  
 Glu Thr Val Leu Ser Leu Gln Lys Thr Thr Leu Ile Pro Gly Gly  
 1100 1105 1110  
 Ser Glu Ser Leu Val Tyr Thr Thr Leu Ser Gly Gly Ile Gly Ile  
 1115 1120 1125  
 Leu Val Pro Phe Thr Ser His Glu Asp His Asp Phe Phe Gln His  
 1130 1135 1140  
 Val Glu Met His Leu Arg Ser Glu His Pro Pro Leu Cys Gly Arg  
 1145 1150 1155  
 Asp His Leu Ser Phe Arg Ser Tyr Tyr Phe Pro Val Lys Asn Val  
 1160 1165 1170  
 Ile Asp Gly Asp Leu Cys Glu Gln Phe Asn Ser Met Glu Pro Asn  
 1175 1180 1185  
 Lys Gln Lys Asn Val Ser Glu Glu Leu Asp Arg Thr Pro Pro Glu  
 1190 1195 1200  
 Val Ser Lys Lys Leu Glu Asp Ile Arg Thr Arg Tyr Ala Phe  
 1205 1210 1215  
 <210> 102  
 <211> 782  
 <212> PRT  
 <213> Homo sapiens  
 <400> 102  
 Met Ala Pro His Arg Pro Ala Pro Ala Leu Leu Cys Ala Leu Ser Leu  
 1 5 10 15  
 Ala Leu Cys Ala Leu Ser Leu Pro Val Arg Ala Ala Thr Ala Ser Arg  
 20 25 30  
 Gly Ala Ser Gln Ala Gly Ala Pro Gln Gly Arg Val Pro Glu Ala Arg  
 35 40 45  
 Pro Asn Ser Met Val Val Glu His Pro Glu Phe Leu Lys Ala Gly Lys  
 50 55 60  
 Glu Pro Gly Leu Gln Ile Trp Arg Val Cys Thr Phe Asp Leu Val Pro

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325 330 335  
 Gly Lys Asp Gly Lys Ile Phe Val Trp Lys Gly Lys Gln Ala Asn Thr  
 340 345 350  
 Glu Glu Arg Lys Ala Ala Leu Lys Thr Ala Ser Asp Phe Ile Thr Lys  
 355 360 365  
 Met Asp Tyr Pro Lys Gln Thr Gln Val Ser Val Leu Pro Glu Gly Gly  
 370 375 380  
 Glu Thr Pro Leu Phe Lys Gln Phe Phe Lys Asn Trp Arg Asp Pro Asp  
 385 390 395 400  
 Gln Thr Asp Gly Leu Gly Leu Ser Tyr Leu Ser Ser His Ile Ala Asn  
 405 410 415  
 Val Glu Arg Val Pro Phe Asp Ala Ala Thr Leu His Thr Ser Thr Ala  
 420 425 430  
 Met Ala Ala Gln His Gly Met Asp Asp Asp Gly Thr Gly Gln Lys Gln  
 435 440 445  
 Ile Trp Arg Ile Glu Gly Ser Asn Lys Val Pro Val Asp Pro Ala Thr  
 450 455 460  
 Tyr Gly Gln Phe Tyr Gly Gly Asp Ser Tyr Ile Ile Leu Tyr Asn Tyr  
 465 470 475 480  
 Arg His Gly Gly Arg Gln Gly Gln Ile Ile Tyr Asn Trp Gln Gly Ala  
 485 490 495  
 Gln Ser Thr Gln Asp Glu Val Ala Ala Ser Ala Ile Leu Thr Ala Gln  
 500 505 510  
 Leu Asp Glu Glu Leu Gly Gly Thr Pro Val Gln Ser Arg Val Val Gln  
 515 520 525  
 Gly Lys Glu Pro Ala His Leu Met Ser Leu Phe Gly Gly Lys Pro Met  
 530 535 540  
 Ile Ile Tyr Lys Gly Gly Thr Ser Arg Glu Gly Gly Gln Thr Ala Pro  
 545 550 555 560  
 Ala Ser Thr Arg Leu Phe Gln Val Arg Ala Asn Ser Ala Gly Ala Thr  
 565 570 575  
 Arg Ala Val Glu Val Leu Pro Lys Ala G Asn Ser Asn Asp



580                      585                      590  
 Ala Phe Val<sub>595</sub> Leu Lys Thr Pro Ser<sub>600</sub> Ala Ala Tyr Leu Trp<sub>605</sub> Val Gly Thr  
 Gly Ala Ser Glu Ala Glu Lys<sub>615</sub> Thr Gly Ala Gln Glu<sub>620</sub> Leu Leu Arg Val  
 Leu Arg Ala Gln Pro Val<sub>630</sub> Gln Val Ala Glu Gly<sub>635</sub> Ser Glu Pro Asp Gly<sub>640</sub>  
 Phe Trp Glu Ala Leu<sub>645</sub> Gly Gly Lys Ala Ala<sub>650</sub> Tyr Arg Thr Ser Pro<sub>655</sub> Arg  
 Leu Lys Asp Lys<sub>660</sub> Lys Met Asp Ala His<sub>665</sub> Pro Pro Arg Leu Phe Ala Cys<sub>670</sub>  
 Ser Asn Lys<sub>675</sub> Ile Gly Arg Phe Val<sub>680</sub> Ile Glu Glu Val Pro<sub>685</sub> Gly Glu Leu  
 Met Gln Glu Asp Leu Ala Thr<sub>695</sub> Asp Asp Val Met Leu<sub>700</sub> Leu Asp Thr Trp  
 Asp Gln Val Phe Val<sub>710</sub> Trp Val Gly Lys Asp Ser<sub>715</sub> Gln Glu Glu Glu Lys<sub>720</sub>  
 Thr Glu Ala Leu Thr<sub>725</sub> Ser Ala Lys Arg Tyr<sub>730</sub> Ile Glu Thr Asp Pro Ala<sub>735</sub>  
 Asn Arg Asp Arg Arg Thr Pro Ile Thr<sub>745</sub> Val Val Lys Gln Gly<sub>750</sub> Phe Glu  
 Pro Pro Ser<sub>755</sub> Phe Val Gly Trp Phe<sub>760</sub> Leu Gly Trp Asp Asp<sub>765</sub> Asp Tyr Trp  
 Ser Val<sub>770</sub> Asp Pro Leu Asp Arg Ala Met Ala Glu Leu<sub>780</sub> Ala Ala

<210> 103  
 <211> 381  
 <212> PRT  
 <213> Homo sapiens

<400> 103

Met Pro Phe Ser Asn Ser His Asn Ala Leu Lys Leu Arg Phe Pro Ala  
 1                      5                      10                      15  
 Glu Asp Glu Phe Pro Asp Leu Ser Ala His Asn Asn His Met Ala Lys  
                     20                      25                      30

Val Leu Thr Pro Glu Leu Tyr Ala Glu Leu Arg Ala Lys Ser Thr Pro  
 35 40 45  
 Ser Gly Phe Thr Leu Asp Asp Val Ile Gln Thr Gly Val Asp Asn Pro  
 50 55 60  
 Gly His Pro Tyr Ile Met Thr Val Gly Cys Val Ala Gly Asp Glu Glu  
 65 70 75 80  
 Ser Tyr Glu Val Phe Lys Asp Leu Phe Asp Pro Ile Ile Glu Asp Arg  
 85 90 95  
 His Gly Gly Tyr Lys Pro Ser Asp Glu His Lys Thr Asp Leu Asn Pro  
 100 105 110  
 Asp Asn Leu Gln Gly Gly Asp Asp Leu Asp Pro Asn Tyr Val Leu Ser  
 115 120 125  
 Ser Arg Val Arg Thr Gly Arg Ser Ile Arg Gly Phe Cys Leu Pro Pro  
 130 135 140  
 His Cys Ser Arg Gly Glu Arg Arg Ala Ile Glu Lys Leu Ala Val Glu  
 145 150 155 160  
 Ala Leu Ser Ser Leu Asp Gly Asp Leu Ala Gly Arg Tyr Tyr Ala Leu  
 165 170 175  
 Lys Ser Met Thr Glu Ala Glu Gln Gln Gln Leu Ile Asp Asp His Phe  
 180 185 190  
 Leu Phe Asp Lys Pro Val Ser Pro Leu Leu Leu Ala Ser Gly Met Ala  
 195 200 205  
 Arg Asp Trp Pro Asp Ala Arg Gly Ile Trp His Asn Asp Asn Lys Thr  
 210 215 220  
 Phe Leu Val Trp Val Asn Glu Glu Asp His Leu Arg Val Ile Ser Met  
 225 230 235 240  
 Gln Lys Gly Gly Asn Met Lys Glu Val Phe Thr Arg Phe Cys Thr Gly  
 245 250 255  
 Leu Thr Gln Ile Glu Thr Leu Phe Lys Ser Lys Asp Tyr Glu Phe Met  
 260 265 270  
 Trp Asn Pro His Leu Gly Tyr Ile Leu Thr Cys Pro Ser Asn Leu Gly  
 275 280 285

Thr Gly Leu Arg Ala Gly Val His Ile Lys Leu Pro Asn Leu Gly Lys  
290 295 300

His Glu Lys Phe Ser Glu Val Leu Lys Arg Leu Arg Leu Gln Lys Arg  
305 310 315 320

Gly Thr Gly Gly Val Asp Thr Ala Ala Val Gly Gly Val Phe Asp Val  
325 330 335

Ser Asn Ala Asp Arg Leu Gly Phe Ser Glu Val Glu Leu Val Gln Met  
340 345 350

Val Val Asp Gly Val Lys Leu Leu Ile Glu Met Glu Gln Arg Leu Glu  
355 360 365

Gln Gly Gln Ala Ile Asp Asp Leu Met Pro Ala Gln Lys  
370 375 380

<210> 104  
<211> 277  
<212> PRT  
<213> Homo sapiens

<400> 104

Met Phe Pro Phe Tyr Ser Cys Trp Arg Thr Gly Leu Leu Leu Leu Leu  
1 5 10 15

Leu Ala Val Ala Val Arg Glu Ser Trp Gln Thr Glu Glu Lys Thr Cys  
20 25 30

Asp Leu Val Gly Glu Lys Gly Lys Glu Ser Glu Lys Glu Leu Ala Leu  
35 40 45

Val Lys Arg Leu Lys Pro Leu Phe Asn Lys Ser Phe Glu Ser Thr Val  
50 55 60

Gly Gln Gly Ser Asp Thr Tyr Ile Tyr Ile Phe Arg Val Cys Arg Glu  
65 70 75 80

Ala Gly Asn His Thr Ser Gly Ala Gly Leu Val Gln Ile Asn Lys Ser  
85 90 95

Asn Gly Lys Glu Thr Val Val Gly Arg Leu Asn Glu Thr His Ile Phe  
100 105 110

Asn Gly Ser Asn Trp Ile Met Leu Ile Tyr Lys Gly Gly Asp Glu Tyr  
115 120 125

Asp Asn His Cys Gly Lys Glu Gln Arg Arg Ala Val Val Met Ile Ser  
 130 135 140

Cys Asn Arg His Thr Leu Ala Asp Asn Phe Asn Pro Val Ser Glu Glu  
 145 150 155 160

Arg Gly Lys Val Gln Asp Cys Phe Tyr Leu Phe Glu Met Asp Ser Ser  
 165 170 175

Leu Ala Cys Ser Pro Glu Ile Ser His Leu Ser Val Gly Ser Ile Leu  
 180 185 190

Leu Val Thr Phe Ala Ser Leu Val Ala Val Tyr Val Val Gly Gly Phe  
 195 200 205

Leu Tyr Gln Arg Leu Val Val Gly Ala Lys Gly Met Glu Gln Phe Pro  
 210 215 220

His Leu Ala Phe Trp Gln Asp Leu Gly Asn Leu Val Ala Asp Gly Cys  
 225 230 235 240

Asp Phe Val Cys Arg Ser Lys Pro Arg Asn Val Pro Ala Ala Tyr Arg  
 245 250 255

Gly Val Gly Asp Asp Gln Leu Gly Glu Glu Ser Glu Glu Arg Asp Asp  
 260 265 270

His Leu Leu Pro Met  
 275

<210> 105  
 <211> 864  
 <212> PRT  
 <213> Homo sapiens

<400> 105

Gln Val Gln His Gly Ser Asn Val Asn Ile His Arg Leu Val Glu Gly  
 1 5 10 15

Asn Val Val Ile Trp Glu Asn Ala Ser Thr Pro Leu Tyr Thr Gly Ala  
 20 25 30

Ile Val Thr Asn Asn Asp Gly Pro Tyr Met Ala Tyr Val Glu Val Leu  
 35 40 45

Gly Asp Pro Asn Leu Gln Phe Phe Ile Lys Ser Gly Asp Ala Trp Val  
 50 55 60

Thr Leu Ser Glu His Glu Tyr Leu Ala Lys Leu Gln Glu Ile Arg Gln  
 65 70 75 80  
 Ala Val His Ile Glu Ser Val Phe Ser Leu Asn Met Ala Phe Gln Leu  
 85 90 95  
 Glu Asn Asn Lys Tyr Glu Val Glu Thr His Ala Lys Asn Gly Ala Asn  
 100 105 110  
 Met Val Thr Phe Ile Pro Arg Asn Gly His Ile Cys Lys Met Val Tyr  
 115 120 125  
 His Lys Asn Val Arg Ile Tyr Lys Ala Thr Gly Asn Asp Thr Val Thr  
 130 135 140  
 Ser Val Val Gly Phe Phe Arg Gly Leu Arg Leu Leu Leu Ile Asn Val  
 145 150 155 160  
 Phe Ser Ile Asp Asp Asn Gly Met Met Ser Asn Arg Tyr Phe Gln His  
 165 170 175  
 Val Asp Asp Lys Tyr Val Pro Ile Ser Gln Lys Asn Tyr Glu Thr Gly  
 180 185 190  
 Ile Val Lys Leu Lys Asp Tyr Lys His Ala Tyr His Pro Val Asp Leu  
 195 200 205  
 Asp Ile Lys Asp Ile Asp Tyr Thr Met Phe His Leu Ala Asp Ala Thr  
 210 215 220  
 Tyr His Glu Pro Cys Phe Lys Ile Ile Pro Asn Thr Gly Phe Cys Ile  
 225 230 235 240  
 Thr Lys Leu Phe Asp Gly Asp Gln Val Leu Tyr Glu Ser Phe Asn Pro  
 245 250 255  
 Leu Ile His Cys Ile Asn Glu Val His Ile Tyr Asp Arg Asn Asn Gly  
 260 265 270  
 Ser Ile Ile Cys Leu His Leu Asn Tyr Ser Pro Pro Ser Tyr Lys Ala  
 275 280 285  
 Tyr Leu Val Leu Lys Asp Thr Gly Trp Glu Ala Thr Thr His Pro Leu  
 290 295 300  
 Leu Glu Glu Lys Ile Glu Glu Leu Gln Asp Gln Arg Ala Cys Glu Leu  
 305 310 315 320

Asp Val Asn Phe Ile Ser Asp Lys Asp Leu Tyr Val Ala Ala Leu Thr  
 325 330 335  
 Asn Ala Asp Leu Asn Tyr Thr Met Val Thr Pro Arg Pro His Arg Asp  
 340 345 350  
 Val Ile Arg Val Ser Asp Gly Ser Glu Val Leu Trp Tyr Tyr Glu Gly  
 355 360 365  
 Leu Asp Asn Phe Leu Val Cys Ala Trp Ile Tyr Val Ser Asp Gly Val  
 370 375 380  
 Ala Ser Leu Val His Leu Arg Ile Lys Asp Arg Ile Pro Ala Asn Asn  
 385 390 395 400  
 Asp Ile Tyr Val Leu Lys Gly Asp Leu Tyr Trp Thr Arg Ile Thr Lys  
 405 410 415  
 Ile Gln Phe Thr Gln Glu Ile Lys Arg Leu Val Lys Lys Ser Lys Lys  
 420 425 430  
 Lys Leu Ala Pro Ile Thr Glu Glu Asp Ser Asp Lys His Asp Glu Pro  
 435 440 445  
 Pro Glu Gly Pro Gly Ala Ser Gly Leu Pro Pro Lys Ala Pro Gly Asp  
 450 455 460  
 Lys Glu Gly Ser Glu Gly His Lys Gly Pro Ser Lys Gly Ser Asp Ser  
 465 470 475 480  
 Ser Lys Glu Gly Lys Lys Pro Gly Ser Gly Lys Lys Pro Gly Pro Ala  
 485 490 495  
 Arg Glu His Lys Pro Ser Lys Ile Pro Thr Leu Ser Lys Lys Pro Ser  
 500 505 510  
 Gly Pro Lys Asp Pro Lys His Pro Arg Asp Pro Lys Glu Pro Arg Lys  
 515 520 525  
 Ser Lys Ser Pro Arg Thr Ala Ser Pro Thr Arg Arg Pro Ser Pro Lys  
 530 535 540  
 Leu Pro Gln Leu Ser Lys Leu Pro Lys Ser Thr Ser Pro Arg Ser Pro  
 545 550 555 560  
 Pro Pro Pro Thr Arg Pro Ser Ser Pro Glu Arg Pro Glu Gly Thr Lys  
 565 570 575

Ile Ile Lys Thr Ser Lys Pro Pro Ser Pro Lys Pro Pro Phe Asp Pro  
 580 585 590  
 Ser Phe Lys Glu Lys Phe Tyr Asp Asp Tyr Ser Lys Ala Ala Ser Arg  
 595 600 605  
 Ser Lys Glu Thr Lys Thr Thr Val Val Leu Asp Glu Ser Phe Glu Ser  
 610 615 620  
 Ile Leu Lys Glu Thr Leu Pro Glu Thr Pro Gly Thr Pro Phe Thr Thr  
 625 630 635 640  
 Pro Arg Pro Val Pro Pro Lys Arg Pro Arg Thr Pro Glu Ser Pro Phe  
 645 650 655  
 Glu Pro Pro Lys Asp Pro Asp Ser Pro Ser Thr Ser Pro Ser Glu Phe  
 660 665 670  
 Phe Thr Pro Pro Glu Ser Lys Arg Thr Arg Phe His Glu Thr Pro Ala  
 675 680 685  
 Asp Thr Pro Leu Pro Asp Val Thr Ala Glu Leu Phe Lys Glu Pro Asp  
 690 695 700  
 Val Thr Ala Glu Thr Lys Ser Pro Asp Glu Ala Met Lys Arg Pro Arg  
 705 710 715 720  
 Ser Pro Ser Glu Tyr Glu Asp Thr Ser Pro Gly Asp Tyr Pro Ser Leu  
 725 730 735  
 Pro Met Lys Arg His Arg Leu Glu Arg Leu Arg Leu Thr Thr Thr Glu  
 740 745 750  
 Met Glu Thr Asp Pro Gly Arg Met Ala Lys Asp Ala Ser Gly Lys Pro  
 755 760 765  
 Val Lys Leu Lys Arg Ser Lys Ser Phe Asp Asp Leu Thr Thr Val Glu  
 770 775 780  
 Leu Ala Pro Glu Pro Lys Ala Ser Arg Ile Val Val Asp Asp Glu Gly  
 785 790 795 800  
 Thr Glu Ala Asp Asp Glu Glu Thr His Pro Pro Glu Glu Arg Gln Lys  
 805 810 815  
 Thr Glu Val Arg Arg Arg Arg Pro Pro Lys Lys Pro Ser Lys Ser Pro  
 820 825 830

Arg Pro Ser Lys Pro Lys Lys Pro Lys Lys Pro Asp Ser Ala Tyr Ile  
835 840 845

Pro Ser Ile Leu Ala Ile Leu Val Val Ser Leu Ile Val Gly Ile Leu  
850 855 860

<210> 106  
<211> 183  
<212> PRT  
<213> Homo sapiens

<400> 106

Met Ala Ser Asn Lys Thr Thr Leu Gln Lys Met Gly Lys Lys Gln Asn  
1 5 10 15

Gly Lys Ser Lys Lys Val Glu Glu Ala Glu Pro Glu Glu Phe Val Val  
20 25 30

Glu Lys Val Leu Asp Arg Arg Val Val Asn Gly Lys Val Glu Tyr Phe  
35 40 45

Leu Lys Trp Lys Gly Phe Thr Asp Ala Asp Asn Thr Trp Glu Pro Glu  
50 55 60

Glu Asn Leu Asp Cys Pro Glu Leu Ile Glu Ala Phe Leu Asn Ser Gln  
65 70 75 80

Lys Ala Gly Lys Glu Lys Asp Gly Thr Lys Arg Lys Ser Leu Ser Asp  
85 90 95

Ser Glu Ser Asp Asp Ser Lys Ser Lys Lys Lys Arg Asp Ala Ala Asp  
100 105 110

Lys Pro Arg Gly Phe Ala Arg Gly Leu Asp Pro Glu Arg Ile Ile Gly  
115 120 125

Ala Ile Asp Ser Ser Gly Glu Leu Met Phe Leu Met Lys Trp Lys Asp  
130 135 140

Ser Asp Glu Ala Asp Leu Val Leu Ala Lys Glu Ala Asn Met Lys Cys  
145 150 155 160

Pro Gln Ile Val Ile Ala Phe Tyr Glu Glu Arg Leu Thr Trp His Ser  
165 170 175

Cys Pro Glu Asp Glu Ala Gln  
180

<210> 107



<211> 1410  
 <212> PRT  
 <213> Homo sapiens

<400> 107

Met Asp Ile Tyr Asp Thr Gln Thr Leu Gly Val Val Val Phe Gly Gly  
 1 5 10 15

Phe Met Val Val Ser Ala Ile Gly Ile Phe Leu Val Ser Thr Phe Ser  
 20 25 30

Met Lys Glu Thr Ser Tyr Glu Glu Ala Leu Ala Asn Gln Arg Lys Glu  
 35 40 45

Met Ala Lys Thr His His Gln Lys Val Glu Lys Lys Lys Lys Glu Lys  
 50 55 60

Thr Val Glu Lys Lys Gly Lys Thr Lys Lys Lys Glu Glu Lys Pro Asn  
 65 70 75 80

Gly Lys Ile Pro Asp His Asp Pro Ala Pro Asn Val Thr Val Leu Leu  
 85 90 95

Arg Glu Pro Val Arg Ala Pro Ala Val Ala Val Ala Pro Thr Pro Val  
 100 105 110

Gln Pro Pro Ile Ile Val Ala Pro Val Ala Thr Val Pro Ala Met Pro  
 115 120 125

Gln Glu Lys Leu Ala Ser Ser Pro Lys Asp Lys Lys Lys Lys Glu Lys  
 130 135 140

Lys Val Ala Lys Val Glu Pro Ala Val Ser Ser Val Val Asn Ser Ile  
 145 150 155 160

Gln Val Leu Thr Ser Lys Ala Ala Ile Leu Glu Thr Ala Pro Lys Glu  
 165 170 175

Val Pro Met Val Val Val pro pro Val Gly Ala Lys Gly Asn Thr Pro  
 180 185 190

Ala Thr Gly Thr Thr Gln Gly Lys Lys Ala Glu Gly Thr Gln Asn Gln  
 195 200 205

Ser Lys Lys Ala Glu Gly Ala Pro Asn Gln Gly Arg Lys Ala Glu Gly  
 210 215 220

Thr Pro Asn Gln Gly Lys Lys Thr Glu Gly Thr Pro Asn Gln Gly Lys  
 225 230 240

Lys Ala Glu Gly Thr Pro Asn Gln Gly Lys Lys Ala Glu Gly Thr Pro  
 245 250 255  
 Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Val  
 260 265 270  
 Asp Thr Thr Pro Asn Gln Gly Lys Lys Val Glu Gly Ala Pro Thr Gln  
 275 280 285  
 Gly Arg Lys Ala Glu Gly Ala Gln Asn Gln Ala Lys Lys Val Glu Gly  
 290 295 300  
 Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys  
 305 310 315 320  
 Lys Gly Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln  
 325 330 335  
 Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala  
 340 345 350  
 Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln  
 355 360 365  
 Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Ser Glu Gly  
 370 375 380  
 Ala Gln Asn Gln Gly Lys Lys Val Glu Gly Ala Gln Asn Gln Gly Lys  
 385 390 395 400  
 Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln  
 405 410 415  
 Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala  
 420 425 430  
 Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln  
 435 440 445  
 Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly  
 450 455 460  
 Ala Gln Asn Gln Gly Lys Lys Val Glu Gly Ala Gln Asn Gln Gly Lys  
 465 470 475 480  
 Lys Ala Glu Gly Ala Gln Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln  
 485 490 495

Asn Gln Gly Lys Lys Ala Glu Gly Ala Gln Asn Gln Gly Gln Lys Gly  
 500 505 510

Glu Gly Ala Gln Asn Gln Gly Lys Lys Thr Glu Gly Ala Gln Gly Lys  
 515 520 525

Lys Ala Glu Arg Ser Pro Asn Gln Gly Lys Lys Gly Glu Gly Ala Pro  
 530 535 540

Ile Gln Gly Lys Lys Ala Asp Ser Val Ala Asn Gln Gly Thr Lys Val  
 545 550 555 560

Glu Gly Ile Thr Asn Gln Gly Lys Lys Ala Glu Gly Ser Pro Ser Glu  
 565 570 575

Gly Lys Lys Ala Glu Gly Ser Pro Asn Gln Gly Lys Lys Ala Asp Ala  
 580 585 590

Ala Ala Asn Gln Gly Lys Lys Thr Glu Ser Ala Ser Val Gln Gly Arg  
 595 600 605

Asn Thr Asp Val Ala Gln Ser Pro Glu Ala Pro Lys Gln Glu Ala Pro  
 610 615 620

Ala Lys Lys Lys Ser Gly Ser Lys Lys Lys Gly Glu Pro Gly Pro Pro  
 625 630 635 640

Asp Ala Asp Gly Pro Leu Tyr Leu Pro Tyr Lys Thr Leu Val Ser Thr  
 645 650 655

Val Gly Ser Met Val Phe Asn Glu Gly Glu Ala Gln Arg Leu Ile Glu  
 660 665 670

Ile Leu Ser Glu Lys Ala Gly Ile Ile Gln Asp Thr Trp His Lys Ala  
 675 680 685

Thr Gln Lys Gly Asp Pro Val Ala Ile Leu Lys Arg Gln Leu Glu Glu  
 690 695 700

Lys Glu Lys Leu Leu Ala Thr Glu Gln Glu Asp Ala Ala Val Ala Lys  
 705 710 715 720

Ser Lys Leu Arg Glu Leu Asn Lys Glu Met Ala Ala Glu Lys Ala Lys  
 725 730 735

Ala Ala Ala Gly Glu Ala Lys Val Lys Lys Gln Leu Val Ala Arg Glu  
 740 745 750

Gln Glu Ile Thr Ala Val Gln Ala Arg Met Gln Ala Ser Tyr Arg Glu  
755 760 765

His Val Lys Glu Val Gln Gln Leu Gln Gly Lys Ile Arg Thr Leu Gln  
770 775 780

Glu Gln Leu Glu Asn Gly Pro Asn Thr Gln Leu Ala Arg Leu Gln Gln  
785 790 795 800

Glu Asn Ser Ile Leu Arg Asp Ala Leu Asn Gln Ala Thr Ser Gln Val  
805 810 815

Glu Ser Lys Gln Asn Ala Glu Leu Ala Lys Leu Arg Gln Glu Leu Ser  
820 825 830

Lys Val Ser Lys Glu Leu Val Glu Lys Ser Glu Ala Val Arg Gln Asp  
835 840 845

Glu Gln Gln Arg Lys Ala Leu Glu Ala Lys Ala Ala Ala Phe Glu Lys  
850 855 860

Gln Val Leu Gln Leu Gln Ala Ser His Arg Glu Ser Glu Glu Ala Leu  
865 870 875 880

Gln Lys Arg Leu Asp Glu Val Ser Arg Glu Leu Cys His Thr Gln Ser  
885 890 895

Ser His Ala Ser Leu Arg Ala Asp Ala Glu Lys Ala Gln Glu Gln Gln  
900 905 910

Gln Gln Met Ala Glu Leu His Ser Lys Leu Gln Ser Ser Glu Ala Glu  
915 920 925

Val Arg Ser Lys Cys Glu Glu Leu Ser Gly Leu His Gly Gln Leu Gln  
930 935 940

Glu Ala Arg Ala Glu Asn Ser Gln Leu Thr Glu Arg Ile Arg Ser Ile  
945 950 955 960

Glu Ala Leu Leu Glu Ala Gly Gln Ala Arg Asp Ala Gln Asp Val Gln  
965 970 975

Ala Ser Gln Ala Glu Ala Asp Gln Gln Gln Thr Arg Leu Lys Glu Leu  
980 985 990

Glu Ser Gln Val Ser Gly Leu Glu Lys Glu Ala Ile Glu Leu Arg Glu  
995 1000 1005

Ala Val Glu Gln Gln Lys Val Lys Asn Asn Asp Leu Arg Glu Lys  
 1010 1015 1020  
 Asn Trp Lys Ala Met Glu Ala Leu Ala Thr Ala Glu Gln Ala Cys  
 1025 1030 1035  
 Lys Glu Lys Leu Leu Ser Leu Thr Gln Ala Lys Glu Glu Ser Glu  
 1040 1045 1050  
 Lys Gln Leu Cys Leu Ile Glu Ala Gln Thr Met Glu Ala Leu Leu  
 1055 1060 1065  
 Ala Leu Leu Pro Glu Leu Ser Val Leu Ala Gln Gln Asn Tyr Thr  
 1070 1075 1080  
 Glu Trp Leu Gln Asp Leu Lys Glu Lys Gly Pro Thr Leu Leu Lys  
 1085 1090 1095  
 His Pro Pro Ala Pro Ala Glu Pro Ser Ser Asp Leu Ala Ser Lys  
 1100 1105 1110  
 Leu Arg Glu Ala Glu Glu Thr Gln Ser Thr Leu Gln Ala Glu Cys  
 1115 1120 1125  
 Asp Gln Tyr Arg Ser Ile Leu Ala Glu Thr Glu Gly Met Leu Arg  
 1130 1135 1140  
 Asp Leu Gln Lys Ser Val Glu Glu Glu Glu Gln Val Trp Arg Ala  
 1145 1150 1155  
 Lys Val Gly Ala Ala Glu Glu Glu Leu Gln Lys Ser Arg Val Thr  
 1160 1165 1170  
 Val Lys His Leu Glu Glu Ile Val Glu Lys Leu Lys Gly Glu Leu  
 1175 1180 1185  
 Glu Ser Ser Asp Gln Val Arg Glu His Thr Ser His Leu Glu Ala  
 1190 1195 1200  
 Glu Leu Glu Lys His Met Ala Ala Ala Ser Ala Glu Cys Gln Asn  
 1205 1210 1215  
 Tyr Ala Lys Glu Val Ala Gly Leu Arg Gln Leu Leu Leu Glu Ser  
 1220 1225 1230  
 Gln Ser Gln Leu Asp Ala Ala Lys Ser Glu Ala Gln Lys Gln Ser  
 1235 1240 1245

Asp Glu Leu Ala Leu Val Arg Gln Gln Leu Ser Glu Met Lys Ser  
1250 1255 1260

His Val Glu Asp Gly Asp Ile Ala Gly Ala Pro Ala Ser Ser Pro  
1265 1270 1275

Glu Ala Pro Pro Ala Glu Gln Asp Pro Val Gln Leu Lys Thr Gln  
1280 1285 1290

Leu Glu Trp Thr Glu Ala Ile Leu Glu Asp Glu Gln Thr Gln Arg  
1295 1300 1305

Gln Lys Leu Thr Ala Glu Phe Glu Glu Ala Gln Thr Ser Ala Cys  
1310 1315 1320

Arg Leu Gln Glu Glu Leu Glu Lys Leu Arg Thr Ala Gly Pro Leu  
1325 1330 1335

Glu Ser Ser Glu Thr Glu Glu Ala Ser Gln Leu Lys Glu Arg Leu  
1340 1345 1350

Glu Lys Glu Lys Lys Leu Thr Ser Asp Leu Gly Arg Ala Ala Thr  
1355 1360 1365

Arg Leu Gln Glu Leu Leu Lys Thr Thr Gln Glu Gln Leu Ala Arg  
1370 1375 1380

Glu Lys Asp Thr Val Lys Lys Leu Gln Glu Gln Leu Glu Lys Ala  
1385 1390 1395

Glu Asp Gly Ser Ser Ser Lys Glu Gly Thr Ser Val  
1400 1405 1410

<210> 108  
<211> 864  
<212> PRT  
<213> Homo sapiens

<400> 108

Gln Val Gln His Gly Ser Asn Val Asn Ile His Arg Leu Val Glu Gly  
1 5 10 15

Asn Val Val Ile Trp Glu Asn Ala Ser Thr Pro Leu Tyr Thr Gly Ala  
20 25 30

Ile Val Thr Asn Asn Asp Gly Pro Tyr Met Ala Tyr Val Glu Val Leu  
35 40 45

Gly Asp Pro Asn Leu Gln Phe Phe Ile Lys Ser Gly Asp Ala Trp Val  
 50 55 60  
 Thr Leu Ser Glu His Glu Tyr Leu Ala Lys Leu Gln Glu Ile Arg Gln  
 65 70 75 80  
 Ala Val His Ile Glu Ser Val Phe Ser Leu Asn Met Ala Phe Gln Leu  
 85 90 95  
 Glu Asn Asn Lys Tyr Glu Val Glu Thr His Ala Lys Asn Gly Ala Asn  
 100 105 110  
 Met Val Thr Phe Ile Pro Arg Asn Gly His Ile Cys Lys Met Val Tyr  
 115 120 125  
 His Lys Asn Val Arg Ile Tyr Lys Ala Thr Gly Asn Asp Thr Val Thr  
 130 135 140  
 Ser Val Val Gly Phe Phe Arg Gly Leu Arg Leu Leu Leu Ile Asn Val  
 145 150 155 160  
 Phe Ser Ile Asp Asp Asn Gly Met Met Ser Asn Arg Tyr Phe Gln His  
 165 170 175  
 Val Asp Asp Lys Tyr Val Pro Ile Ser Gln Lys Asn Tyr Glu Thr Gly  
 180 185 190  
 Ile Val Lys Leu Lys Asp Tyr Lys His Ala Tyr His Pro Val Asp Leu  
 195 200 205  
 Asp Ile Lys Asp Ile Asp Tyr Thr Met Phe His Leu Ala Asp Ala Thr  
 210 215 220  
 Tyr His Glu Pro Cys Phe Lys Ile Ile Pro Asn Thr Gly Phe Cys Ile  
 225 230 235 240  
 Thr Lys Leu Phe Asp Gly Asp Gln Val Leu Tyr Glu Ser Phe Asn Pro  
 245 250 255  
 Leu Ile His Cys Ile Asn Glu Val His Ile Tyr Asp Arg Asn Asn Gly  
 260 265 270  
 Ser Ile Ile Cys Leu His Leu Asn Tyr Ser Pro Pro Ser Tyr Lys Ala  
 275 280 285  
 Tyr Leu Val Leu Lys Asp Thr Gly Trp Glu Ala Thr Thr His Pro Leu  
 290 295 300

Leu Glu Glu Lys Ile Glu Glu Leu Gln Asp Gln Arg Ala Cys Glu Leu  
 305 310 315 320  
 Asp Val Asn Phe Ile Ser Asp Lys Asp Leu Tyr Val Ala Ala Leu Thr  
 325 330 335  
 Asn Ala Asp Leu Asn Tyr Thr Met Val Thr Pro Arg Pro His Arg Asp  
 340 345 350  
 Val Ile Arg Val Ser Asp Gly Ser Glu Val Leu Trp Tyr Tyr Glu Gly  
 355 360 365  
 Leu Asp Asn Phe Leu Val Cys Ala Trp Ile Tyr Val Ser Asp Gly Val  
 370 375 380  
 Ala Ser Leu Val His Leu Arg Ile Lys Asp Arg Ile Pro Ala Asn Asn  
 385 390 395 400  
 Asp Ile Tyr Val Leu Lys Gly Asp Leu Tyr Trp Thr Arg Ile Thr Lys  
 405 410 415  
 Ile Gln Phe Thr Gln Glu Ile Lys Arg Leu Val Lys Lys Ser Lys Lys  
 420 425 430  
 Lys Leu Ala Pro Ile Thr Glu Glu Asp Ser Asp Lys His Asp Glu Pro  
 435 440 445  
 Pro Glu Gly Pro Gly Ala Ser Gly Leu Pro Pro Lys Ala Pro Gly Asp  
 450 455 460  
 Lys Glu Gly Ser Glu Gly His Lys Gly Pro Ser Lys Gly Ser Asp Ser  
 465 470 475 480  
 Ser Lys Glu Gly Lys Lys Pro Gly Ser Gly Lys Lys Pro Gly Pro Ala  
 485 490 495  
 Arg Glu His Lys Pro Ser Lys Ile Pro Thr Leu Ser Lys Lys Pro Ser  
 500 505 510  
 Gly Pro Lys Asp Pro Lys His Pro Arg Asp Pro Lys Glu Pro Arg Lys  
 515 520 525  
 Ser Lys Ser Pro Arg Thr Ala Ser Pro Thr Arg Arg Pro Ser Pro Lys  
 530 535 540  
 Leu Pro Gln Leu Ser Lys Leu Pro Lys Ser Thr Ser Pro Arg Ser Pro  
 545 550 555 560



Pro Pro Pro Thr Arg Pro Ser Ser Pro Glu Arg Pro Glu Gly Thr Lys  
 565 570 575  
 Ile Ile Lys Thr Ser Lys Pro Pro Ser Pro Lys Pro Pro Phe Asp Pro  
 580 585 590  
 Ser Phe Lys Glu Lys Phe Tyr Asp Asp Tyr Ser Lys Ala Ala Ser Arg  
 595 600 605  
 Ser Lys Glu Thr Lys Thr Thr Val Val Leu Asp Glu Ser Phe Glu Ser  
 610 615 620  
 Ile Leu Lys Glu Thr Leu Pro Glu Thr Pro Gly Thr Pro Phe Thr Thr  
 625 630 635 640  
 Pro Arg Pro Val Pro Pro Lys Arg Pro Arg Thr Pro Glu Ser Pro Phe  
 645 650 655  
 Glu Pro Pro Lys Asp Pro Asp Ser Pro Ser Thr Ser Pro Ser Glu Phe  
 660 665 670  
 Phe Thr Pro Pro Glu Ser Lys Arg Thr Arg Phe His Glu Thr Pro Ala  
 675 680 685  
 Asp Thr Pro Leu Pro Asp Val Thr Ala Glu Leu Phe Lys Glu Pro Asp  
 690 695 700  
 Val Thr Ala Glu Thr Lys Ser Pro Asp Glu Ala Met Lys Arg Pro Arg  
 705 710 715 720  
 Ser Pro Ser Glu Tyr Glu Asp Thr Ser Pro Gly Asp Tyr Pro Ser Leu  
 725 730 735  
 Pro Met Lys Arg His Arg Leu Glu Arg Leu Arg Leu Thr Thr Thr Glu  
 740 745 750  
 Met Glu Thr Asp Pro Gly Arg Met Ala Lys Asp Ala Ser Gly Lys Pro  
 755 760 765  
 Val Lys Leu Lys Arg Ser Lys Ser Phe Asp Asp Leu Thr Thr Val Glu  
 770 775 780  
 Leu Ala Pro Glu Pro Lys Ala Ser Arg Ile Val Val Asp Asp Glu Gly  
 785 790 795 800  
 Thr Glu Ala Asp Asp Glu Glu Thr His Pro Pro Glu Glu Arg Gln Lys  
 805 810 815

Thr Glu Val Arg Arg Arg Arg Pro Pro Lys Lys Pro Ser Lys Ser Pro  
820 825 830

Arg Pro Ser Lys Pro Lys Lys Pro Lys Lys Pro Asp Ser Ala Tyr Ile  
835 840 845

Pro Ser Ile Leu Ala Ile Leu Val Val Ser Leu Ile Val Gly Ile Leu  
850 855 860

<210> 109  
<211> 588  
<212> PRT  
<213> Homo sapiens

<400> 109

Gln Leu Asn Glu Glu Met Glu Ala Lys Gln Asn Leu Glu Arg His Ile  
1 5 10 15

Ser Thr Leu Asn Ile Gln Leu Ser Asp Ser Lys Lys Lys Leu Gln Asp  
20 25 30

Phe Ala Ser Thr Val Glu Ala Leu Glu Glu Gly Lys Lys Arg Phe Gln  
35 40 45

Lys Glu Ile Glu Asn Leu Thr Gln Gln Tyr Glu Glu Lys Ala Ala Ala  
50 55 60

Tyr Asp Lys Leu Glu Lys Thr Lys Asn Arg Leu Gln Gln Glu Leu Asp  
65 70 75 80

Asp Leu Val Val Asp Leu Asp Asn Gln Arg Gln Leu Val Ser Asn Leu  
85 90 95

Glu Lys Lys Gln Arg Lys Phe Asp Gln Leu Leu Ala Glu Glu Lys Asn  
100 105 110

Ile Ser Ser Lys Tyr Ala Asp Glu Arg Asp Arg Ala Glu Ala Glu Ala  
115 120 125

Arg Glu Lys Glu Thr Lys Ala Leu Ser Leu Ala Arg Ala Leu Glu Glu  
130 135 140

Ala Leu Glu Ala Lys Glu Glu Leu Glu Arg Thr Asn Lys Met Leu Lys  
145 150 155 160

Ala Glu Met Glu Asp Leu Val Ser Ser Lys Asp Asp Val Gly Lys Asn  
165 170 175

Val His Glu Leu Glu Lys Ser Lys Arg Ala Leu Glu Thr Gln Met Glu  
 180 185 190  
 Glu Met Lys Thr Gln Leu Glu Glu Leu Glu Asp Glu Leu Gln Ala Thr  
 195 200 205  
 Glu Asp Ala Lys Leu Arg Leu Glu Val Asn Met Gln Ala Leu Lys Gly  
 210 215 220  
 Gln Phe Glu Arg Asp Leu Gln Ala Arg Asp Glu Gln Asn Glu Glu Lys  
 225 230 235 240  
 Arg Arg Gln Leu Gln Arg Gln Leu His Glu Tyr Glu Thr Glu Leu Glu  
 245 250 255  
 Asp Glu Arg Lys Gln Arg Ala Leu Ala Ala Ala Lys Lys Lys Leu  
 260 265 270  
 Glu Gly Asp Leu Lys Asp Leu Glu Leu Gln Ala Asp Ser Ala Ile Lys  
 275 280 285  
 Gly Arg Glu Glu Ala Ile Lys His Val Arg Lys Leu Gln Ala Gln Met  
 290 295 300  
 Lys Asp Phe Gln Arg Glu Leu Glu Asp Ala Arg Ala Ser Arg Asp Glu  
 305 310 315 320  
 Ile Phe Ala Thr Ala Lys Glu Asn Glu Lys Lys Ala Lys Ser Leu Glu  
 325 330 335  
 Ala Asp Leu Met Gln Leu Gln Glu Asp Leu Ala Ala Ala Glu Arg Ala  
 340 345 350  
 Arg Lys Gln Ala Asp Leu Glu Lys Glu Glu Leu Ala Glu Glu Leu Ala  
 355 360 365  
 Ser Ser Leu Ser Gly Arg Asn Ala Leu Gln Asp Glu Lys Arg Arg Leu  
 370 375 380  
 Glu Ala Arg Ile Ala Gln Leu Glu Glu Glu Leu Glu Glu Glu Gln Gly  
 385 390 395 400  
 Asn Met Glu Ala Met Ser Asp Arg Val Arg Lys Ala Thr Gln Gln Ala  
 405 410 415  
 Glu Gln Leu Ser Asn Glu Leu Ala Thr Glu Arg Ser Thr Ala Gln Lys  
 420 425 430

Asn Glu Ser Ala Arg Gln Gln Leu Glu Arg Gln Asn Lys Glu Leu Arg  
435 440 445

Ser Lys Leu His Glu Met Glu Gly Ala Val Lys Ser Lys Phe Lys Ser  
450 455 460

Thr Ile Ala Ala Leu Glu Ala Lys Ile Ala Gln Leu Glu Glu Gln Val  
465 470 475 480

Glu Gln Glu Ala Arg Glu Lys Gln Ala Ala Thr Lys Ser Leu Lys Gln  
485 490 495

Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu Gln Val Glu Asp Glu Arg  
500 505 510

Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala Glu Lys Gly Asn Ala Arg  
515 520 525

Val Lys Gln Leu Lys Arg Gln Leu Glu Glu Ala Glu Glu Glu Ser Gln  
530 535 540

Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln Arg Glu Leu Asp Glu Ala  
545 550 555 560

Thr Glu Ser Asn Glu Ala Met Gly Arg Glu Val Asn Ala Leu Lys Ser  
565 570 575

Lys Leu Arg Gly Pro Pro Pro Gln Glu Thr Ser Gln  
580 585

<210> 110  
<211> 119  
<212> PRT  
<213> Homo sapiens

<400> 110.

Met Ala Gly Arg Gly Lys Leu Thr Ala Val Ile Gly Asp Glu Asp Thr  
1 5 10 15

Val Thr Gly Phe Leu Leu Gly Gly Ile Gly Glu Leu Asn Lys Asn Arg  
20 25 30

His Pro Asn Phe Leu Val Val Glu Lys Asp Thr Thr Ile Asn Glu Ile  
35 40 45

Glu Asp Thr Phe Arg Gln Phe Leu Asn Arg Asp Asp Ile Gly Ile Ile  
50 55 60

Leu Ile Asn Gln Tyr Ile Ala Glu Met Val Arg His Ala Leu Asp Ala

65                      70                      75                      80  
 His Gln Gln Ser Ile Pro Ala Val Leu Glu Ile Pro Ser Lys Glu His  
                                  85                                   90                                   95  
 Pro Tyr Asp Ala Ala Lys Asp Ser Ile Leu Arg Arg Ala Arg Gly Met  
                                  100                                   105                                   110  
 Phe Thr Ala Glu Asp Leu Arg  
                                  115  
 <210> 111  
 <211> 356  
 <212> PRT  
 <213> Homo sapiens  
 <400> 111  
 Ala Ala Ala Ala Lys Pro Asn Asn Leu Ser Leu Val Val His Gly Pro  
 1                                   5                                   10                                   15  
 Gly Asp Leu Arg Leu Glu Asn Tyr Pro Ile Pro Glu Pro Gly Pro Asn  
                                  20                                   25                                   30  
 Glu Val Leu Leu Arg Met His Ser Val Gly Ile Cys Gly Ser Asp Val  
                                  35                                   40                                   45  
 His Tyr Trp Glu Tyr Gly Arg Ile Gly Asn Phe Ile Val Lys Lys Pro  
                                  50                                   55                                   60  
 Met Val Leu Gly His Glu Ala Ser Gly Thr Val Glu Lys Val Gly Ser  
 65                                   70                                   75                                   80  
 Ser Val Lys His Leu Lys Pro Gly Asp Arg Val Ala Ile Glu Pro Gly  
                                  85                                   90                                   95  
 Ala Pro Arg Glu Asn Asp Glu Phe Cys Lys Met Gly Arg Tyr Asn Leu  
                                  100                                   105                                   110  
 Ser Pro Ser Ile Phe Phe Cys Ala Thr Pro Pro Asp Asp Gly Asn Leu  
                                  115                                   120                                   125  
 Cys Arg Phe Tyr Lys His Asn Ala Ala Phe Cys Tyr Lys Leu Pro Asp  
                                  130                                   135                                   140  
 Asn Val Thr Phe Glu Glu Gly Ala Leu Ile Glu Pro Leu Ser Val Gly  
 145                                   150                                   155                                   160  
 Ile His Ala Cys Arg Arg Gly Gly Val Thr Leu Gly His Lys Val Leu  
                                  165                                   170                                   175

Val Cys Gly Ala Gly Pro Ile Gly Met Val Thr Leu Leu Val Ala Lys  
 180 185 190  
 Ala Met Gly Ala Ala Gln Val Val Val Thr Asp Leu Ser Ala Thr Arg  
 195 200 205  
 Leu Ser Lys Ala Lys Glu Ile Gly Ala Asp Leu Val Leu Gln Ile Ser  
 210 215 220  
 Lys Glu Ser Pro Gln Glu Ile Ala Arg Lys Val Glu Gly Leu Leu Gly  
 225 230 235 240  
 Cys Lys Pro Glu Val Thr Ile Glu Cys Thr Gly Ala Glu Ala Ser Ile  
 245 250 255  
 Gln Ala Gly Ile Tyr Ala Thr Arg Ser Gly Gly Thr Leu Val Leu Val  
 260 265 270  
 Gly Leu Gly Ser Glu Met Thr Thr Val Pro Leu Leu His Ala Ala Ile  
 275 280 285  
 Arg Glu Val Asp Ile Lys Gly Val Phe Arg Tyr Cys Asn Thr Trp Pro  
 290 295 300  
 Val Ala Ile Ser Met Leu Ala Ser Lys Ser Val Asn Val Lys Pro Leu  
 305 310 315 320  
 Val Thr His Arg Phe Pro Leu Glu Lys Ala Leu Glu Ala Phe Glu Thr  
 325 330 335  
 Phe Lys Lys Gly Leu Gly Leu Lys Ile Met Leu Lys Cys Asp Pro Ser  
 340 345 350  
 Asp Gln Asn Pro  
 355

<210> 112  
 <211> 914  
 <212> PRT  
 <213> Homo sapiens

<400> 112

Met Ser Gln Ser Gln Asn Ala Ile Phe Thr Ser Pro Thr Gly Glu Glu  
 1 5 10 15  
 Asn Leu Met Asn Ser Asn His Arg Asp Ser Glu Ser Ile Thr Asp Val  
 20 25 30

Cys Ser Asn Glu Asp Leu Pro Glu Val Glu Leu Val Ser Leu Leu Glu  
 35 40 45  
 Glu Gln Leu Pro Gln Tyr Arg Leu Lys Val Asp Thr Leu Phe Leu Tyr  
 50 55 60  
 Glu Asn Gln Asp Trp Thr Gln Ser Pro His Gln Arg Gln His Ala Ser  
 65 70 75 80  
 Asp Ala Leu Ser Pro Val Leu Ala Glu Glu Thr Phe Arg Tyr Met Ile  
 85 90 95  
 Leu Gly Thr Asp Arg Val Glu Gln Met Thr Lys Thr Tyr Asn Asp Ile  
 100 105 110  
 Asp Met Val Thr His Leu Leu Ala Glu Arg Asp Arg Asp Leu Glu Leu  
 115 120 125  
 Ala Ala Arg Ile Gly Gln Ala Leu Leu Lys Arg Asn His Val Leu Ser  
 130 135 140  
 Glu Gln Asn Glu Ser Leu Glu Glu Gln Leu Gly Gln Ala Phe Asp Gln  
 145 150 155 160  
 Val Asn Gln Leu Gln His Glu Leu Cys Lys Lys Asp Glu Leu Leu Arg  
 165 170 175  
 Ile Val Ser Ile Ala Ser Glu Glu Ser Glu Thr Asp Ser Ser Cys Ser  
 180 185 190  
 Thr Pro Leu Arg Phe Asn Glu Ser Phe Ser Leu Ser Gln Gly Leu Leu  
 195 200 205  
 Gln Leu Glu Met Leu Gln Glu Lys Leu Lys Glu Leu Glu Glu Asn  
 210 215 220  
 Met Ala Leu Arg Ser Lys Ala Cys His Ile Lys Thr Glu Thr Val Thr  
 225 230 235 240  
 Tyr Glu Glu Lys Glu Gln Gln Leu Val Ser Asp Cys Val Lys Glu Leu  
 245 250 255  
 Arg Glu Thr Asn Ala Gln Met Ser Arg Met Thr Glu Glu Leu Ser Gly  
 260 265 270  
 Lys Ser Asp Glu Leu Ile Arg Tyr Gln Glu Glu Leu Ser Ser Leu Leu  
 275 280 285

Ser Gln Ile Val Asp Leu Gln His Lys Leu Lys Glu His Val Ile Glu  
 290 295 300  
 Lys Glu Glu Leu Lys Leu His Leu Gln Ala Ser Lys Asp Ala Gln Arg  
 305 310 315 320  
 Gln Leu Thr Met Glu Leu His Glu Leu Gln Asp Arg Asn Met Glu Cys  
 325 330 335  
 Leu Gly Met Leu His Glu Ser Gln Glu Glu Ile Lys Glu Leu Arg Ser  
 340 345 350  
 Arg Ser Gly Pro Thr Ala His Leu Tyr Phe Ser Gln Ser Tyr Gly Ala  
 355 360 365  
 Phe Thr Gly Glu Ser Leu Ala Ala Glu Ile Glu Gly Thr Met Arg Lys  
 370 375 380  
 Lys Leu Ser Leu Asp Glu Glu Ser Ser Leu Phe Lys Gln Lys Ala Gln  
 385 390 395 400  
 Gln Lys Arg Val Phe Asp Thr Val Arg Ile Ala Asn Asp Thr Arg Gly  
 405 410 415  
 Arg Ser Ile Ser Phe Pro Ala Leu Leu Pro Ile Pro Gly Ser Asn Arg  
 420 425 430  
 Ser Ser Val Ile Met Thr Ala Lys Pro Phe Glu Ser Gly Leu Gln Gln  
 435 440 445  
 Thr Glu Asp Lys Ser Leu Leu Asn Gln Gly Ser Ser Ser Glu Glu Val  
 450 455 460  
 Ala Gly Ser Ser Gln Lys Met Gly Gln Pro Gly Pro Ser Gly Asp Ser  
 465 470 475 480  
 Asp Leu Ala Thr Ala Leu His Arg Leu Ser Leu Arg Arg Gln Asn Tyr  
 485 490 495  
 Leu Ser Glu Lys Gln Phe Phe Ala Glu Glu Trp Gln Arg Lys Ile Gln  
 500 505 510  
 Val Leu Ala Asp Gln Lys Glu Gly Val Ser Gly Cys Val Thr Pro Thr  
 515 520 525  
 Glu Ser Leu Ala Ser Leu Cys Thr Thr Gln Ser Glu Ile Thr Asp Leu  
 530 535 540



Ser Ser Ala Ser Cys Leu Arg Gly Phe Met Pro Glu Lys Leu Gln Ile  
 545 550 555 560  
 Val Lys Pro Leu Glu Gly Ser Gln Thr Leu Tyr His Trp Gln Gln Leu  
 565 570 575  
 Ala Gln Pro Asn Leu Gly Thr Ile Leu Asp Pro Arg Pro Gly Val Ile  
 580 585 590  
 Thr Lys Gly Phe Thr Gln Leu Pro Gly Asp Ala Ile Tyr His Ile Ser  
 595 600 605  
 Asp Leu Glu Glu Asp Glu Glu Glu Gly Ile Thr Phe Gln Val Gln Gln  
 610 615 620  
 Pro Leu Glu Val Glu Glu Lys Leu Ser Thr Ser Lys Pro Val Thr Gly  
 625 630 635 640  
 Ile Phe Leu Pro Pro Ile Thr Ser Ala Gly Gly Pro Val Thr Val Ala  
 645 650 655  
 Thr Ala Asn Pro Gly Lys Cys Leu Ser Cys Thr Asn Ser Thr Phe Thr  
 660 665 670  
 Phe Thr Thr Cys Arg Ile Leu His Pro Ser Asp Ile Thr Gln Val Thr  
 675 680 685  
 Pro Ser Ser Gly Phe Pro Ser Leu Ser Cys Gly Ser Ser Gly Ser Ser  
 690 695 700  
 Ser Ser Asn Thr Ala Val Asn Ser Pro Ala Leu Ser Tyr Arg Leu Ser  
 705 710 715 720  
 Ile Gly Glu Ser Ile Thr Asn Arg Arg Asp Ser Thr Thr Thr Phe Ser  
 725 730 735  
 Ser Thr Met Ser Leu Ala Lys Leu Leu Gln Glu Arg Gly Ile Ser Ala  
 740 745 750  
 Lys Val Tyr His Ser Pro Ile Ser Glu Asn Pro Leu Gln Pro Leu Pro  
 755 760 765  
 Lys Ser Leu Ala Ile Pro Ser Thr Pro Pro Asn Ser Pro Ser His Ser  
 770 775 780  
 Pro Cys Pro Ser Pro Leu pro Phe Glu Pro Arg Val His Leu Ser Glu  
 785 790 795 800

Asn phe Leu Ala Ser Arg Pro Ala Glu Thr Phe Leu Gln Glu Met Tyr  
 805 810 815

Gly Leu Arg Pro Ser Arg Asn Pro Pro Asp Val Gly Gln Leu Lys Met  
 820 825 830

Asn Leu Val Asp Arg Leu Lys Arg Leu Gly Ile Ala Arg Val Val Lys  
 835 840 845

Asn Pro Gly Ala Gln Glu Asn Gly Arg Cys Gln Glu Ala Glu Ile Gly  
 850 855 860

Pro Gln Lys Pro Asp Ser Ala Val Tyr Leu Asn Ser Gly Ser Ser Leu  
 865 870 875 880

Leu Gly Gly Leu Arg Arg Asn Gln Ser Leu Pro Val Ile Met Gly Ser  
 885 890 895

Phe Ala Ala Pro Val Cys Thr Ser Ser Pro Lys Met Gly Val Leu Lys  
 900 905 910

Glu Asp

<210> 113  
 <211> 264  
 <212> PRT  
 <213> Homo sapiens

<400> 113

Met Glu Ala Phe Leu Gly Ser Arg Ser Gly Leu Trp Ala Gly Gly Pro  
 1 5 10 15

Ala Pro Gly Gln Phe Tyr Arg Ile Pro Ser Thr Pro Asp Ser Phe Met  
 20 25 30

Asp Pro Ala Ser Ala Leu Tyr Arg Gly Pro Ile Thr Arg Thr Gln Asn  
 35 40 45

Pro Met Val Thr Gly Thr Ser Val Leu Gly Val Lys Phe Glu Gly Gly  
 50 55 60

Val Val Ile Ala Ala Asp Met Leu Gly Ser Tyr Gly Ser Leu Ala Arg  
 65 70 75 80

Phe Arg Asn Ile Ser Arg Ile Met Arg Val Asn Asn Ser Thr Met Leu  
 85 90 95

Gly Ala Ser Gly Asp Tyr Ala Asp Phe Gln Tyr Leu Lys Gln Val Leu  
 100 105 110

Gly Gln Met Val Ile Asp Glu Glu Leu Leu Gly Asp Gly His Ser Tyr  
 115 120 125

Ser Pro Arg Ala Ile His Ser Trp Leu Thr Arg Ala Met Tyr Ser Arg  
 130 135 140

Arg Ser Lys Met Asn Pro Leu Trp Asn Thr Met Val Ile Gly Gly Tyr  
 145 150 155 160

Ala Asp Gly Glu Ser Phe Leu Gly Tyr Val Asp Met Leu Gly Val Ala  
 165 170 175

Tyr Glu Ala Pro Ser Leu Ala Thr Gly Tyr Gly Ala Tyr Leu Ala Gln  
 180 185 190

Pro Leu Leu Arg Glu Val Leu Glu Lys Gln Pro Val Leu Ser Gln Thr  
 195 200 205

Glu Ala Arg Asp Leu Val Glu Arg Cys Met Arg Val Leu Tyr Tyr Arg  
 210 215 220

Asp Ala Arg Ser Tyr Asn Arg Phe Gln Thr Ala Thr Val Thr Glu Lys  
 225 230 235 240

Gly Val Glu Ile Glu Gly Pro Leu Ser Thr Glu Thr Asn Trp Asp Ile  
 245 250 255

Ala His Met Ile Ser Gly Phe Glu  
 260

<210> 114  
 <211> 1464  
 <212> PRT  
 <213> Homo sapiens

<400> 114

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Ala Ala Thr  
 1 5 10 15

Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln Val Glu Gly Gln Asp  
 20 25 30

Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn Gly Leu Arg Tyr His  
 35 40 45

Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp

50                      55                      60  
 Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn  
 65                      70                      75                      80  
 Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro  
 85                      90                      95  
 Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly  
 100                      105                      110  
 Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro  
 115                      120                      125  
 Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro Gly Pro Pro  
 130                      135                      140  
 Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala  
 145                      150                      155                      160  
 Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser Thr Gly Gly Ile Ser  
 165                      170                      175  
 Val Pro Gly Pro Met Gly Pro Ser Gly Pro Arg Gly Leu Pro Gly Pro  
 180                      185                      190  
 Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro  
 195                      200                      205  
 Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly  
 210                      215                      220  
 Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg  
 225                      230                      235                      240  
 Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly Leu Pro  
 245                      250                      255  
 Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe Ser Gly  
 260                      265                      270  
 Leu Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu  
 275                      280                      285  
 Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg  
 290                      295                      300  
 Gly Leu Pro Gly Glu Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly

305                      310                      315                      320  
 Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro  
                                  325                                   330                                   335  
 Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala Lys  
                                  340                                   345                                   350  
 Gly Glu Ala Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly Pro Gln Gly  
                                  355                                   360                                   365  
 Val Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Ala Ala Gly Pro  
                                  370                                   375                                   380  
 Ala Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Ala Asn  
                                  385                                   390                                   395                                   400  
 Gly Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly  
                                  405                                   410                                   415  
 Pro Ser Gly Pro Gln Gly Pro Gly Gly Pro Pro Gly Pro Lys Gly Asn  
                                  420                                   425                                   430  
 Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys  
                                  435                                   440                                   445  
 Gly Glu Pro Gly Pro Val Gly Val Gln Gly Pro Pro Gly Pro Ala Gly  
                                  450                                   455                                   460  
 Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Thr Gly Leu  
                                  465                                   470                                   475                                   480  
 Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro  
                                  485                                   490                                   495  
 Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly  
                                  500                                   505                                   510  
 Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg  
                                  515                                   520                                   525  
 Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro  
                                  530                                   535                                   540  
 Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly  
                                  545                                   550                                   555                                   560  
 Gln Asp Gly Arg Pro Gly Pro Pro Gly P       -       -       Ala Arg Gly Gln

565 570 575

Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro  
580 585 590

Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly  
595 600 605

Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro  
610 615 620

Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro  
625 630 635 640

Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly  
645 650 655

Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro  
660 665 670

Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln  
675 680 685

Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly  
690 695 700

Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser  
705 710 715 720

Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala  
725 730 735

Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly  
740 745 750

Ala Asp Gly Ser Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro  
755 760 765

Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ser  
770 775 780

Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly  
785 790 795 800

Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro  
805 810 815

Pro Gly Ala Asp Gly Gln Pro Gly Ala Pro Gly Asp Ala

820	825	830
Gly Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly	840	845
835		
Pro Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala	855	860
850		
Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala	870	875
865		880
Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly	885	890
		895
Pro Pro Gly Pro Ala Gly Lys Glu Gly Gly Lys Gly Pro Arg Gly Glu	900	905
		910
Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro	915	920
		925
Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly	930	935
		940
Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val	945	950
		955
Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro	965	970
		975
Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly	980	985
		990
Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro	995	1000
		1005
Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Gly Ala Glu Gly Ser	1010	1015
		1020
Pro Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu	1025	1030
		1035
Thr Gly Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala	1040	1045
		1050
Pro Gly Pro Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu	1055	1060
		1065
Thr Gly Pro Ala Gly Pro Ala Gly Pro Ala Gly Ala		

1070	1075	1080
Arg Gly 1085	Pro Ala Gly Pro Gln 1090	Gly Pro Arg Gly Asp Lys Gly Glu 1095
Thr Gly 1100	Glu Gln Gly Asp Arg 1105	Gly Ile Lys Gly His Arg Gly Phe 1110
Ser Gly 1115	Leu Gln Gly Pro Pro 1120	Gly Pro Pro Gly Ser Pro Gly Glu 1125
Gln Gly 1130	Pro Ser Gly Ala Ser 1135	Gly Pro Ala Gly Pro Arg Gly Pro 1140
Pro Gly 1145	Ser Ala Gly Ala Pro 1150	Gly Lys Asp Gly Leu Asn Gly Leu 1155
Pro Gly 1160	Pro Ile Gly Pro Pro 1165	Gly Pro Arg Gly Arg Thr Gly Asp 1170
Ala Gly 1175	Pro Val Gly Pro Pro 1180	Gly Pro Pro Gly Pro Gly Pro 1185
Pro Gly 1190	Pro Pro Ser Ala Gly 1195	Phe Asp Phe Ser Phe Leu Pro Gln 1200
Pro Pro 1205	Gln Glu Lys Ala His 1210	Asp Gly Gly Arg Tyr Tyr Arg Ala 1215
Asp Asp 1220	Ala Asn Val Val Arg 1225	Asp Arg Asp Leu Glu Val Asp Thr 1230
Thr Leu 1235	Lys Ser Leu Ser Gln 1240	Gln Ile Glu Asn Ile Arg Ser Pro 1245
Glu Gly 1250	Ser Arg Lys Asn Pro 1255	Ala Arg Thr Cys Arg Asp Leu Lys 1260
Met Cys 1265	His Ser Asp Trp Lys 1270	Ser Gly Glu Tyr Trp Ile Asp Pro 1275
Asn Gln 1280	Gly Cys Asn Leu Asp 1285	Ala Ile Lys Val Phe Cys Asn Met 1290
Glu Thr 1295	Gly Glu Thr Cys Val 1300	Tyr Pro Thr Gln Pro Ser Val Ala 1305
Gln Lys	Asn Trp Tyr Ile Ser Lys Asn	ip Lys Arg His



1310                      1315                      1320  
 Val Trp Phe Gly Glu Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr  
     1325                      1330                      1335  
 Gly Gly Gln Gly Ser Asp Pro Ala Asp Val Ala Ile Gln Leu Thr  
     1340                      1345                      1350  
 Phe Leu Arg Leu Met Ser Thr Glu Ala Ser Gln Asn Ile Thr Tyr  
     1355                      1360                      1365  
 His Cys Lys Asn Ser Val Ala Tyr Met Asp Gln Gln Thr Gly Asn  
     1370                      1375                      1380  
 Leu Lys Lys Ala Leu Leu Leu Lys Gly Ser Asn Glu Ile Glu Ile  
     1385                      1390                      1395  
 Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr Ser Val Thr Val Asp  
     1400                      1405                      1410  
 Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys Thr Val Ile Glu  
     1415                      1420                      1425  
 Tyr Lys Thr Thr Lys Thr Ser Arg Leu Pro Ile Ile Asp Val Ala  
     1430                      1435                      1440  
 Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe Asp Val  
     1445                      1450                      1455  
 Gly Pro Val Cys Phe Leu  
     1460

<210> 115  
 <211> 108  
 <212> PRT  
 <213> Homo sapiens

<400> 115

Met Ile Leu Gln Arg Leu Phe Arg Phe Ser Ser Val Ile Arg Ser Ala  
 1                      5                      10                      15  
 Val Ser Val His Leu Arg Arg Asn Ile Gly Val Thr Ala Val Ala Phe  
     20                      25                      30  
 Asn Lys Glu Leu Asp Pro Ile Gln Lys Leu Phe Val Asp Lys Ile Arg  
     35                      40                      45  
 Glu Tyr Lys Ser Lys Arg Gln Thr Ser Gly Gly Pro Val Asp Ala Ser  
     50                      55                      60

Ser Glu Tyr Gln Gln Glu Leu Glu Arg Glu Leu Phe Lys Leu Lys Gln  
65 70 75 80

Met Phe Gly Asn Ala Asp Met Asn Thr Phe Pro Thr Phe Lys Phe Glu  
85 90 95

Asp Pro Lys Phe Glu Val Ile Glu Lys Pro Gln Ala  
100 105

<210> 116  
<211> 1210  
<212> PRT  
<213> Homo sapiens

<400> 116

Met Ala Ala Ala Ala Gly Ala Ala Ala Ala Ala Ala Glu Gly Glu  
1 5 10 15

Ala Pro Ala Glu Met Gly Ala Leu Leu Leu Glu Lys Glu Thr Arg Gly  
20 25 30

Ala Thr Glu Arg Val His Gly Ser Leu Gly Asp Thr Pro Arg Ser Glu  
35 40 45

Glu Thr Leu Pro Lys Ala Asn Pro Asp Ser Leu Glu Pro Ala Gly Pro  
50 55 60

Ser Ser Pro Ala Ser Val Thr Val Thr Val Gly Asp Glu Gly Ala Asp  
65 70 75 80

Thr Pro Val Gly Ala Thr Pro Leu Ile Gly Asp Glu Ser Glu Asn Leu  
85 90 95

Glu Gly Asp Gly Asp Leu Arg Gly Gly Arg Ile Leu Leu Gly His Ala  
100 105 110

Thr Lys Ser Phe Pro Ser Ser Pro Ser Lys Gly Gly Ser Cys Pro Ser  
115 120 125

Arg Ala Lys Met Ser Met Thr Gly Ala Gly Lys Ser Pro Pro Ser Val  
130 135 140

Gln Ser Leu Ala Met Arg Leu Leu Ser Met Pro Gly Ala Gln Gly Ala  
145 150 155 160

Ala Ala Ala Gly Ser Glu Pro Pro Pro Ala Thr Thr Ser Pro Glu Gly  
165 170 175

Gln Pro Lys Val His Arg Ala Arg Lys Thr Met Ser Lys Pro Gly Asn  
 180 185 190  
 Gly Gln Pro Pro Val Pro Glu Lys Arg Pro Pro Glu Ile Gln His Phe  
 195 200 205  
 Arg Met Ser Asp Asp Val His Ser Leu Gly Lys Val Thr Ser Asp Leu  
 210 215 220  
 Ala Lys Arg Arg Lys Leu Asn Ser Gly Gly Gly Leu Ser Glu Glu Leu  
 225 230 235 240  
 Gly Ser Ala Arg Arg Ser Gly Glu Val Thr Leu Thr Lys Gly Asp Pro  
 245 250 255  
 Gly Ser Leu Glu Glu Trp Glu Thr Val Val Gly Asp Asp Phe Ser Leu  
 260 265 270  
 Tyr Tyr Asp Ser Tyr Ser Val Asp Glu Arg Val Asp Ser Asp Ser Lys  
 275 280 285  
 Ser Glu Val Glu Ala Leu Thr Glu Gln Leu Ser Glu Glu Glu Glu  
 290 295 300  
 Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu  
 305 310 315 320  
 Glu Glu Glu Asp Glu Glu Ser Gly Asn Gln Ser Asp Arg Ser Gly Ser  
 325 330 335  
 Ser Gly Arg Arg Lys Ala Lys Lys Lys Trp Arg Lys Asp Ser Pro Trp  
 340 345 350  
 Val Lys Pro Ser Arg Lys Arg Arg Lys Arg Glu Pro Pro Arg Ala Lys  
 355 360 365  
 Glu Pro Arg Gly Val Asn Gly Val Gly Ser Ser Gly Pro Ser Glu Tyr  
 370 375 380  
 Met Glu Val Pro Leu Gly Ser Leu Glu Leu Pro Ser Glu Gly Thr Leu  
 385 390 395 400  
 Ser Pro Asn His Ala Gly Val Ser Asn Asp Thr Ser Ser Leu Glu Thr  
 405 410 415  
 Glu Arg Gly Phe Glu Glu Leu Pro Leu Cys Ser Cys Arg Met Glu Ala  
 420 425 430

Pro Lys Ile Asp Arg Ile Ser Glu Arg Ala Gly His Lys Cys Met Ala  
435 440 445

Thr Glu Ser Val Asp Gly Glu Leu Ser Gly Cys Asn Ala Ala Ile Leu  
450 455 460

Lys Arg Glu Thr Met Arg Pro Ser Ser Arg Val Ala Leu Met Val Leu  
465 470 475 480

Cys Glu Thr His Arg Ala Arg Met Val Lys His His Cys Cys Pro Gly  
485 490 495

Cys Gly Tyr Phe Cys Thr Ala Gly Thr Phe Leu Glu Cys His Pro Asp  
500 505 510

Phe Arg Val Ala His Arg Phe His Lys Ala Cys Val Ser Gln Leu Asn  
515 520 525

Gly Met Val Phe Cys Pro His Cys Gly Glu Asp Ala Ser Glu Ala Gln  
530 535 540

Glu Val Thr Ile Pro Arg Gly Asp Gly Val Thr Pro Pro Ala Gly Thr  
545 550 555 560

Ala Ala Pro Ala Pro Pro Pro Leu Ser Gln Asp Val Pro Gly Arg Ala  
565 570 575

Asp Thr Ser Gln Pro Ser Ala Arg Met Arg Gly His Gly Glu Pro Arg  
580 585 590

Arg Pro Pro Cys Asp Pro Leu Ala Asp Thr Ile Asp Ser Ser Gly Pro  
595 600 605

Ser Leu Thr Leu Pro Asn Gly Gly Cys Leu Ser Ala Val Gly Leu Pro  
610 615 620

Leu Gly Pro Gly Arg Glu Ala Leu Glu Lys Ala Leu Val Ile Gln Glu  
625 630 635 640

Ser Glu Arg Arg Lys Lys Leu Arg Phe His Pro Arg Gln Leu Tyr Leu  
645 650 655

Ser Val Lys Gln Gly Glu Leu Gln Lys Val Ile Leu Met Leu Leu Asp  
660 665 670

Asn Leu Asp Pro Asn Phe Gln Ser Asp Gln Gln Ser Lys Arg Thr Pro  
675 680 685

Leu His Ala Ala Ala Gln Lys Gly Ser Val Glu Ile Cys His Val Leu  
 690 695 700  
 Leu Gln Ala Gly Ala Asn Ile Asn Ala Val Asp Lys Gln Gln Arg Thr  
 705 710 715 720  
 Pro Leu Met Glu Ala Val Val Asn Asn His Leu Glu Val Ala Arg Tyr  
 725 730 735  
 Met Val Gln Arg Gly Gly Cys Val Tyr Ser Lys Glu Glu Asp Gly Ser  
 740 745 750  
 Thr Cys Leu His His Ala Ala Lys Ile Gly Asn Leu Glu Met Val Ser  
 755 760 765  
 Leu Leu Leu Ser Thr Gly Gln Val Asp Val Asn Ala Gln Asp Ser Gly  
 770 775 780  
 Gly Trp Thr Pro Ile Ile Trp Ala Ala Glu His Lys His Ile Glu Val  
 785 790 795 800  
 Ile Arg Met Leu Leu Thr Arg Gly Ala Asp Val Thr Leu Thr Asp Asn  
 805 810 815  
 Glu Glu Asn Ile Cys Leu His Trp Ala Ser Phe Thr Gly Ser Ala Ala  
 820 825 830  
 Ile Ala Glu Val Leu Leu Asn Ala Arg Cys Asp Leu His Ala Val Asn  
 835 840 845  
 Tyr His Gly Asp Thr Pro Leu His Ile Ala Ala Arg Glu Ser Tyr His  
 850 855 860  
 Asp Cys Val Leu Leu Phe Leu Ser Arg Gly Ala Asn Pro Glu Leu Arg  
 865 870 875 880  
 Asn Lys Glu Gly Asp Thr Ala Trp Asp Leu Thr Pro Glu Arg Ser Asp  
 885 890 895  
 Val Trp Phe Ala Leu Gln Leu Asn Arg Lys Leu Arg Leu Gly Val Gly  
 900 905 910  
 Asn Arg Ala Ile Arg Thr Glu Lys Ile Ile Cys Arg Asp Val Ala Arg  
 915 920 925  
 Gly Tyr Glu Asn Val Pro Ile Pro Cys Val Asn Gly Val Asp Gly Glu  
 930 935 940

Pro Cys Pro Glu Asp Tyr Lys Tyr Ile Ser Glu Asn Cys Glu Thr Ser  
945 950 955 960

Thr Met Asn Ile Asp Arg Asn Ile Thr His Leu Gln His Cys Thr Cys  
965 970 975

Val Asp Asp Cys Ser Ser Ser Asn Cys Leu Cys Gly Gln Leu Ser Ile  
980 985 990

Arg Cys Trp Tyr Asp Lys Asp Gly Arg Leu Leu Gln Glu Phe Asn Lys  
995 1000 1005

Ile Glu Pro Pro Leu Ile Phe Glu Cys Asn Gln Ala Cys Ser Cys  
1010 1015 1020

Trp Arg Asn Cys Lys Asn Arg Val Val Gln Ser Gly Ile Lys Val  
1025 1030 1035

Arg Leu Gln Leu Tyr Arg Thr Ala Lys Met Gly Trp Gly Val Arg  
1040 1045 1050

Ala Leu Gln Thr Ile Pro Gln Gly Thr Phe Ile Cys Glu Tyr Val  
1055 1060 1065

Gly Glu Leu Ile Ser Asp Ala Glu Ala Asp Val Arg Glu Asp Asp  
1070 1075 1080

Ser Tyr Leu Phe Asp Leu Asp Asn Lys Asp Gly Glu Val Tyr Cys  
1085 1090 1095

Ile Asp Ala Arg Tyr Tyr Gly Asn Ile Ser Arg Phe Ile Asn His  
1100 1105 1110

Leu Cys Asp Pro Asn Ile Ile Pro Val Arg Val Phe Met Leu His  
1115 1120 1125

Gln Asp Leu Arg Phe Pro Arg Ile Ala Phe Phe Ser Ser Arg Asp  
1130 1135 1140

Ile Arg Thr Gly Glu Glu Leu Gly Phe Asp Tyr Gly Asp Arg Phe  
1145 1150 1155

Trp Asp Ile Lys Ser Lys Tyr Phe Thr Cys Gln Cys Gly Ser Glu  
1160 1165 1170

Lys Cys Lys His Ser Ala Glu Ala Ile Ala Leu Glu Gln Ser Arg  
1175 1180 1185

Leu Ala Arg Leu Asp Pro His Pro Glu Leu Leu Pro Glu Leu Gly  
 1190 1195 1200

Ser Leu Pro Pro Val Asn Thr  
 1205 1210

<210> 117  
 <211> 937  
 <212> PRT  
 <213> Homo sapiens

<400> 117

Met Glu Lys Met Leu Ala Gly Cys Phe Leu Leu Ile Leu Gly Gln Ile  
 1 5 10 15

Val Leu Leu Pro Ala Glu Ala Arg Glu Arg Ser Arg Gly Arg Ser Ile  
 20 25 30

Ser Arg Gly Arg His Ala Arg Thr His Pro Gln Thr Ala Leu Leu Glu  
 35 40 45

Ser Ser Cys Glu Asn Lys Arg Ala Asp Leu Val Phe Ile Ile Asp Ser  
 50 55 60

Ser Arg Ser Val Asn Thr His Asp Tyr Ala Lys Val Lys Glu Phe Ile  
 65 70 75 80

Val Asp Ile Leu Gln Phe Leu Asp Ile Gly Pro Asp Val Thr Arg Val  
 85 90 95

Gly Leu Leu Gln Tyr Gly Ser Thr Val Lys Asn Glu Phe Ser Leu Lys  
 100 105 110

Thr Phe Lys Arg Lys Ser Glu Val Glu Arg Ala Val Lys Arg Met Arg  
 115 120 125

His Leu Ser Thr Gly Thr Met Thr Gly Leu Ala Ile Gln Tyr Ala Leu  
 130 135 140

Asn Ile Ala Phe Ser Glu Ala Glu Gly Ala Arg Pro Leu Arg Glu Asn  
 145 150 155 160

Val Pro Arg Val Ile Met Ile Val Thr Asp Gly Arg Pro Gln Asp Ser  
 165 170 175

Val Ala Glu Val Ala Ala Lys Ala Arg Asp Thr Gly Ile Leu Ile Phe  
 180 185 190

Ala Ile Gly Val Gly Gln Val Asp Phe Asn Thr Leu Lys Ser Ile Gly  
 195 200 205  
 Ser Glu Pro His Glu Asp His Val Phe Leu Val Ala Asn Phe Ser Gln  
 210 215 220  
 Ile Glu Thr Leu Thr Ser Val Phe Gln Lys Lys Leu Cys Thr Ala His  
 225 230 235 240  
 Met Cys Ser Thr Leu Glu His Asn Cys Ala His Phe Cys Ile Asn Ile  
 245 250 255  
 Pro Gly Ser Tyr Val Cys Arg Cys Lys Gln Gly Tyr Ile Leu Asn Ser  
 260 265 270  
 Asp Gln Thr Thr Cys Arg Ile Gln Asp Leu Cys Ala Met Glu Asp His  
 275 280 285  
 Asn Cys Glu Gln Leu Cys Val Asn Val Pro Gly Ser Phe Val Cys Gln  
 290 295 300  
 Cys Tyr Ser Gly Tyr Ala Leu Ala Glu Asp Gly Lys Arg Cys Val Ala  
 305 310 315 320  
 Val Asp Tyr Cys Ala Ser Glu Asn His Gly Cys Glu His Glu Cys Val  
 325 330 335  
 Asn Ala Asp Gly Ser Tyr Leu Cys Gln Cys His Glu Gly Phe Ala Leu  
 340 345 350  
 Asn Pro Asp Glu Lys Thr Cys Thr Lys Ile Asp Tyr Cys Ala Ser Ser  
 355 360 365  
 Asn His Gly Cys Gln His Glu Cys Val Asn Thr Asp Asp Ser Tyr Ser  
 370 375 380  
 Cys His Cys Leu Lys Gly Phe Thr Leu Asn Pro Asp Lys Lys Thr Cys  
 385 390 395 400  
 Arg Arg Ile Asn Tyr Cys Ala Leu Asn Lys Pro Gly Cys Glu His Glu  
 405 410 415  
 Cys Val Asn Met Glu Glu Ser Tyr Tyr Cys Arg Cys His Arg Gly Tyr  
 420 425 430  
 Thr Leu Asp Pro Asn Gly Lys Thr Cys Ser Arg Val Asp His Cys Ala  
 435 440 445



Gln Gln Asp His Gly Cys Glu Gln Leu Cys Leu Asn Thr Glu Asp Ser  
450 455 460

Phe Val Cys Gln Cys Ser Glu Gly Phe Leu Ile Asn Glu Asp Leu Lys  
465 470 475 480

Thr Cys Ser Arg Val Asp Tyr Cys Leu Leu Ser Asp His Gly Cys Glu  
485 490 495

Tyr Ser Cys Val Asn Met Asp Arg Ser Phe Ala Cys Gln Cys Pro Glu  
500 505 510

Gly His Val Leu Arg Ser Asp Gly Lys Thr Cys Ala Lys Leu Asp Ser  
515 520 525

Cys Ala Leu Gly Asp His Gly Cys Glu His Ser Cys Val Ser Ser Glu  
530 535 540

Asp Ser Phe Val Cys Gln Cys Phe Glu Gly Tyr Ile Leu Arg Glu Asp  
545 550 555 560

Gly Lys Thr Cys Arg Arg Lys Asp Val Cys Gln Ala Ile Asp His Gly  
565 570 575

Cys Glu His Ile Cys Val Asn Ser Asp Asp Ser Tyr Thr Cys Glu Cys  
580 585 590

Leu Glu Gly Phe Arg Leu Ala Glu Asp Gly Lys Arg Cys Arg Arg Lys  
595 600 605

Asp Val Cys Lys Ser Thr His His Gly Cys Glu His Ile Cys Val Asn  
610 615 620

Asn Gly Asn Ser Tyr Ile Cys Lys Cys Ser Glu Gly Phe Val Leu Ala  
625 630 635 640

Glu Asp Gly Arg Arg Cys Lys Lys Cys Thr Glu Gly Pro Ile Asp Leu  
645 650 655

Val Phe Val Ile Asp Gly Ser Lys Ser Leu Gly Glu Glu Asn Phe Glu  
660 665 670

Val Val Lys Gln Phe Val Thr Gly Ile Ile Asp Ser Leu Thr Ile Ser  
675 680 685

Pro Lys Ala Ala Arg Val Gly Leu Leu Gln Tyr Ser Thr Gln Val His  
690 695 700

Thr Glu Phe Thr Leu Arg Asn Phe Asn Ser Ala Lys Asp Met Lys Lys  
705 710 715 720

Ala Val Ala His Met Lys Tyr Met Gly Lys Gly Ser Met Thr Gly Leu  
725 730 735

Ala Leu Lys His Met Phe Glu Arg Ser Phe Thr Gln Gly Glu Gly Ala  
740 745 750

Arg Pro Leu Ser Thr Arg Val Pro Arg Ala Ala Ile Val Phe Thr Asp  
755 760 765

Gly Arg Ala Gln Asp Asp Val Ser Glu Trp Ala Ser Lys Ala Lys Ala  
770 775 780

Asn Gly Ile Thr Met Tyr Ala Val Gly Val Gly Lys Ala Ile Glu Glu  
785 790 795 800

Glu Leu Gln Glu Ile Ala Ser Glu Pro Thr Asn Lys His Leu Phe Tyr  
805 810 815

Ala Glu Asp Phe Ser Thr Met Asp Glu Ile Ser Glu Lys Leu Lys Lys  
820 825 830

Gly Ile Cys Glu Ala Leu Glu Asp Ser Asp Gly Arg Gln Asp Ser Pro  
835 840 845

Ala Gly Glu Leu Pro Lys Thr Val Gln Gln Pro Thr Val Gln His Arg  
850 855 860

Tyr Leu Phe Glu Glu Asp Asn Leu Leu Arg Ser Thr Gln Lys Leu Ser  
865 870 875 880

His Ser Thr Lys Pro Ser Gly Ser Pro Leu Glu Glu Lys His Asp Gln  
885 890 895

Cys Lys Cys Glu Asn Leu Ile Met Phe Gln Asn Leu Ala Asn Glu Glu  
900 905 910

Val Arg Lys Leu Thr Gln Arg Leu Glu Glu Met Thr Gln Arg Met Glu  
915 920 925

Ala Leu Glu Asn Arg Leu Arg Tyr Arg  
930 935

<210> 118  
<211> 182  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 118

Met Pro Arg Val Val Pro Asp Gln Arg Ser Lys Phe Glu Asn Glu Glu  
 1 5 10 15

Phe Phe Arg Lys Leu Ser Arg Glu Cys Glu Ile Lys Tyr Thr Gly Phe  
 20 25 30

Arg Asp Arg Pro His Glu Glu Arg Gln Ala Arg Phe Gln Asn Ala Cys  
 35 40 45

Arg Asp Gly Arg Ser Glu Ile Ala Phe Val Ala Thr Gly Thr Asn Leu  
 50 55 60

Ser Leu Gln Phe Phe Pro Ala Ser Trp Gln Gly Glu Gln Arg Gln Thr  
 65 70 75 80

Pro Ser Arg Glu Tyr Val Asp Leu Glu Arg Glu Ala Gly Lys Val Tyr  
 85 90 95

Leu Lys Ala Pro Met Ile Leu Asn Gly Val Cys Val Ile Trp Lys Gly  
 100 105 110

Trp Ile Asp Leu Gln Arg Leu Asp Gly Met Gly Cys Leu Glu Phe Asp  
 115 120 125

Glu Glu Arg Ala Gln Gln Glu Asp Ala Leu Ala Gln Gln Ala Phe Glu  
 130 135 140

Glu Ala Arg Arg Arg Thr Arg Glu Phe Glu Asp Arg Asp Arg Ser His  
 145 150 155 160

Arg Glu Glu Met Glu Val Arg Val Ser Gln Leu Leu Ala Val Thr Gly  
 165 170 175

Lys Lys Thr Thr Arg Pro  
 180

&lt;210&gt; 119

&lt;211&gt; 1366

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 119

Met Leu Ser Phe Val Asp Thr Arg Thr Leu Leu Leu Leu Ala Val Thr  
 1 5 10 15

Leu Cys Leu Ala Thr Cys Gln Ser Leu Gln Glu Glu Thr Val Arg Lys  
 20 25 30

Gly Pro Ala Gly Asp Arg Gly Pro Arg Gly Glu Arg Gly Pro Pro Gly  
 35 40 45  
 Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro  
 50 55 60  
 Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln  
 65 70 75 80  
 Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met  
 85 90 95  
 Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly  
 100 105 110  
 Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro  
 115 120 125  
 Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp  
 130 135 140  
 Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly  
 145 150 155 160  
 Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe  
 165 170 175  
 Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro  
 180 185 190  
 Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly  
 195 200 205  
 Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg  
 210 215 220  
 Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val  
 225 230 235 240  
 Gly Pro Val Gly Pro Ala Gly Pro Asn Gly Ser Ala Gly Pro Pro Gly  
 245 250 255  
 Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn  
 260 265 270  
 Ala Gly Pro Thr Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro  
 275 280 285

Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly  
 290 295 300  
 Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala  
 305 310 315 320  
 Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala  
 325 330 335  
 Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly  
 340 345 350  
 Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro  
 355 360 365  
 Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn  
 370 375 380  
 Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Gly Leu Arg Gly  
 385 390 395 400  
 Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val  
 405 410 415  
 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg  
 420 425 430  
 Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly  
 435 440 445  
 Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys  
 450 455 460  
 Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile  
 465 470 475 480  
 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly  
 485 490 495  
 Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His  
 500 505 510  
 Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn  
 515 520 525  
 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly  
 530 535 540

Glu Gln Gly Pro Asp Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro  
 545 550 555 560  
 Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His  
 565 570 575  
 Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly  
 580 585 590  
 Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser  
 595 600 605  
 Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro  
 610 615 620  
 Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly  
 625 630 635 640  
 Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu  
 645 650 655  
 Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp  
 660 665 670  
 Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly  
 675 680 685  
 Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro  
 690 695 700  
 Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala  
 705 710 715 720  
 Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly  
 725 730 735  
 Ala Lys Gly Glu Arg Gly Gly Lys Gly Pro Lys Gly Glu Asn Gly Val  
 740 745 750  
 Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn  
 755 760 765  
 Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly  
 770 775 780  
 Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro  
 785 790 795 800

Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu  
805 810 815

Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly  
820 825 830

Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro  
835 840 845

Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln  
850 855 860

Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly  
865 870 875 880

Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro  
885 890 895

Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val  
900 905 910

Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly  
915 920 925

Asn Pro Gly Asn Asp Gly Pro Pro Gly Arg Asp Gly Gln Pro Gly His  
930 935 940

Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala  
945 950 955 960

Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly  
965 970 975

Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala  
980 985 990

Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys  
995 1000 1005

Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Phe Lys  
1010 1015 1020

Gly His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His  
1025 1030 1035

Gly Asp Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg  
1040 1045 1050

Gly Pro Ala Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr  
 1055 1060 1065  
 Gly His Pro Gly Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln  
 1070 1075 1080  
 Gly His Gln Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro  
 1085 1090 1095  
 Gly Pro Pro Gly Val Ser Gly Gly Gly Tyr Asp Phe Gly Tyr Asp  
 1100 1105 1110  
 Gly Asp Phe Tyr Arg Ala Asp Gln Pro Arg Ser Ala Pro Ser Leu  
 1115 1120 1125  
 Arg Pro Lys Asp Tyr Glu Val Asp Ala Thr Leu Lys Ser Leu Asn  
 1130 1135 1140  
 Asn Gln Ile Glu Thr Leu Leu Thr Pro Glu Gly Ser Arg Lys Asn  
 1145 1150 1155  
 Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu Ser His Pro Glu Trp  
 1160 1165 1170  
 Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln Gly Cys Thr Met  
 1175 1180 1185  
 Glu Ala Ile Lys Val Tyr Cys Asp Phe Pro Thr Gly Glu Thr Cys  
 1190 1195 1200  
 Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp Tyr Arg  
 1205 1210 1215  
 Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile Asn  
 1220 1225 1230  
 Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys  
 1235 1240 1245  
 Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr  
 1250 1255 1260  
 Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr  
 1265 1270 1275  
 Met Asp Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln  
 1280 1285 1290



Gly Ser Asn Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe  
1295 1300 1305

Thr Tyr Thr Val Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu  
1310 1315 1320

Trp Gly Lys Thr Ile Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg  
1325 1330 1335

Leu Pro Phe Leu Asp Ile Ala Pro Leu Asp Ile Gly Gly Ala Asp  
1340 1345 1350

His Glu Phe Phe Val Asp Ile Gly Pro Val Cys Phe Lys  
1355 1360 1365

<210> 120  
<211> 350  
<212> PRT  
<213> Homo sapiens

<400> 120

Gly Asn Ala Ala Thr Ala Lys Lys Gly Ser Glu Val Glu Ser Val Lys  
1 5 10 15

Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu Lys Lys Trp Glu Asn  
20 25 30

Pro Thr Gln Asn Asn Ala Gly Leu Glu Asp Phe Glu Arg Lys Lys Thr  
35 40 45

Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys Ala  
50 55 60

Thr Glu Gln Tyr Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val Val  
65 70 75 80

Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu Gln  
85 90 95

Ala Val Asn Phe Pro Phe Leu Val Arg Leu Glu Tyr Ala Phe Lys Asp  
100 105 110

Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Pro Gly Gly Glu Met  
115 120 125

Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala Arg  
130 135 140

Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser Leu  
145 150 155 160

Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp His  
165 170 175

Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val Lys  
180 185 190

Gly Arg Thr Trp Thr Leu Cys Gly Thr Pro Glu Tyr Leu Ala Pro Glu  
195 200 205

Ile Ile Leu Ser Lys Gly Tyr Asn Lys Ala Val Asp Trp Trp Ala Leu  
210 215 220

Gly Val Leu Ile Tyr Glu Met Ala Ala Gly Tyr Pro Pro Phe Phe Ala  
225 230 235 240

Asp Gln Pro Ile Gln Ile Tyr Glu Lys Ile Val Ser Gly Lys Val Arg  
245 250 255

Phe Pro Ser His Phe Ser Ser Asp Leu Lys Asp Leu Leu Arg Asn Leu  
260 265 270

Leu Gln Val Asp Leu Thr Lys Arg Phe Gly Asn Leu Lys Asn Gly Val  
275 280 285

Ser Asp Ile Lys Thr His Lys Trp Phe Ala Thr Thr Asp Trp Ile Ala  
290 295 300

Ile Tyr Gln Arg Lys Val Glu Ala Pro Phe Ile Pro Lys Phe Arg Gly  
305 310 315 320

Ser Gly Asp Thr Ser Asn Phe Asp Asp Tyr Glu Glu Glu Asp Ile Arg  
325 330 335

Val ser Ile Thr Glu Lys Cys Ala Lys Glu Phe Gly Glu Phe  
340 345 350

<210> 121  
<211> 987  
<212> PRT  
<213> Homo sapiens

<400> 121

Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu  
1 5 10 15

Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp  
 20 25 30  
 Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu  
 35 40 45  
 Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln  
 50 55 60  
 Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg  
 65 70 75 80  
 Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu  
 85 90 95  
 Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr  
 100 105 110  
 Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro  
 115 120 125  
 Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu  
 130 135 140  
 His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn  
 145 150 155 160  
 Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu  
 165 170 175  
 Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu  
 180 185 190  
 Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro  
 195 200 205  
 Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val  
 210 215 220  
 Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg  
 225 230 235 240  
 Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala  
 245 250 255  
 Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala  
 260 265 270

Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys  
 275 280 285  
 Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys  
 290 295 300  
 Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys  
 305 310 315 320  
 Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly  
 325 330 335  
 Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg  
 340 345 350  
 Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly  
 355 360 365  
 Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg  
 370 375 380  
 Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe  
 385 390 395 400  
 Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala  
 405 410 415  
 Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu  
 420 425 430  
 Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser  
 435 440 445  
 Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Val  
 450 455 460  
 Leu Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser  
 465 470 475 480  
 Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly  
 485 490 495  
 Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg Ser Glu  
 500 505 510  
 Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln Thr Gln Leu  
 515 520 525

Asp Glu Ser Glu Gly Trp Arg Glu Gln Leu Ala Leu Ile Ala Gly Thr  
 530 535 540  
 Ala Val Val Gly Val Val Leu Val Leu Val Val Ile Val Val Ala Val  
 545 550 555 560  
 Leu Cys Leu Arg Lys Gln Ser Asn Gly Arg Glu Ala Glu Tyr Ser Asp  
 565 570 575  
 Lys His Gly Gln Tyr Leu Ile Gly His Gly Thr Lys Val Tyr Ile Asp  
 580 585 590  
 Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala Val Arg Glu Phe Ala Lys  
 595 600 605  
 Glu Ile Asp Val Ser Tyr Val Lys Ile Glu Glu Val Ile Gly Ala Gly  
 610 615 620  
 Glu Phe Gly Glu Val Cys Arg Gly Arg Leu Lys Ala Pro Gly Lys Lys  
 625 630 635 640  
 Glu Ser Cys Val Ala Ile Lys Thr Leu Lys Gly Gly Tyr Thr Glu Arg  
 645 650 655  
 Gln Arg Arg Glu Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Glu  
 660 665 670  
 His Pro Asn Ile Ile Arg Leu Glu Gly Val Val Thr Asn Ser Met Pro  
 675 680 685  
 Val Met Ile Leu Thr Glu Phe Met Glu Asn Gly Ala Leu Asp Ser Phe  
 690 695 700  
 Leu Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met  
 705 710 715 720  
 Leu Arg Gly Ile Ala Ser Gly Met Arg Tyr Leu Ala Glu Met Ser Tyr  
 725 730 735  
 Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu  
 740 745 750  
 Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu Glu Glu Asn  
 755 760 765  
 Ser Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile Pro Ile  
 770 775 780

Arg Trp Thr Ala Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala  
785 790 795 800

Ser Asp Ala Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Phe  
805 810 815

Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Asn Ala  
820 825 830

Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro Pro Asp Cys Pro Thr Ser  
835 840 845

Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Asp Arg Asn Ala Arg  
850 855 860

Pro Arg Phe Pro Gln Val Val Ser Ala Leu Asp Lys Met Ile Arg Asn  
865 870 875 880

Pro Ala Ser Leu Lys Ile Val Ala Arg Glu Asn Gly Gly Ala Ser His  
885 890 895

Pro Leu Leu Asp Gln Arg Gln Pro His Tyr Ser Ala Phe Gly Ser Val  
900 905 910

Gly Glu Trp Leu Arg Ala Ile Lys Met Gly Arg Tyr Glu Glu Ser Phe  
915 920 925

Ala Ala Ala Gly Phe Gly Ser Phe Glu Leu Val Ser Gln Ile Ser Ala  
930 935 940

Glu Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln Lys Lys  
945 950 955 960

Ile Leu Ala Ser Val Gln His Met Lys Ser Gln Ala Lys Pro Gly Thr  
965 970 975

Pro Gly Gly Thr Gly Gly Pro Ala Pro Gln Tyr  
980 985

<210> 122

<211> 774

<212> PRT

<213> Homo sapiens

<400> 122

Met Glu Arg Pro Leu Cys Ser His Leu Cys Ser Cys Leu Ala Met Leu  
1 5 10 15

Ala Leu Leu Ser Pro Leu Ser Leu Ala Gln Tyr Asp Ser Trp Pro His

**319/514**

275                      280                      285  
 Val Thr Cys Glu Asn Gly Leu Pro Ala Val Val Ser Cys Val Pro Gly  
 290                      295                      300  
 Gln Val Phe Ser Pro Asp Gly Pro Ser Arg Phe Arg Lys Ala Tyr Lys  
 305                      310                      315  
 Pro Glu Gln Pro Leu Val Arg Leu Arg Gly Gly Ala Tyr Ile Gly Glu  
 325                      330                      335  
 Gly Arg Val Glu Val Leu Lys Asn Gly Glu Trp Gly Thr Val Cys Asp  
 340                      345                      350  
 Asp Lys Trp Asp Leu Val Ser Ala Ser Val Val Cys Arg Glu Leu Gly  
 355                      360                      365  
 Phe Gly Ser Ala Lys Glu Ala Val Thr Gly Ser Arg Leu Gly Gln Gly  
 370                      375                      380  
 Ile Gly Pro Ile His Leu Asn Glu Ile Gln Cys Thr Gly Asn Glu Lys  
 385                      390                      395  
 Ser Ile Ile Asp Cys Lys Phe Asn Ala Glu Ser Gln Gly Cys Asn His  
 405                      410                      415  
 Glu Glu Asp Ala Gly Val Arg Cys Asn Thr Pro Ala Met Gly Leu Gln  
 420                      425                      430  
 Lys Lys Leu Arg Leu Asn Gly Gly Arg Asn Pro Tyr Glu Gly Arg Val  
 435                      440                      445  
 Glu Val Leu Val Glu Arg Asn Gly Ser Leu Val Trp Gly Met Val Cys  
 450                      455                      460  
 Gly Gln Asn Trp Gly Ile Val Glu Ala Met Val Val Cys Arg Gln Leu  
 465                      470                      475                      480  
 Gly Leu Gly Phe Ala Ser Asn Ala Phe Gln Glu Thr Trp Tyr Trp His  
 485                      490                      495  
 Gly Asp Val Asn Ser Asn Lys Val Val Met Ser Gly Val Lys Cys Ser  
 500                      505                      510  
 Gly Thr Glu Leu Ser Leu Ala His Cys Arg His Asp Gly Glu Asp Val  
 515                      520                      525  
 Ala Cys Pro Gln Gly Gly Val Gln Tyr Gly Ala Gly Val Ala Cys Ser



530                      535                      540  
 Glu Thr Ala Pro Asp Leu Val Leu Asn Ala Glu Met Val Gln Gln Thr  
 545                      550                      555  
 Thr Tyr Leu Glu Asp Arg Pro Met Phe Met Leu Gln Cys Ala Met Glu  
                     565                      570                      575  
 Glu Asn Cys Leu Ser Ala Ser Ala Ala Gln Thr Asp Pro Thr Thr Gly  
                     580                      585                      590  
 Tyr Arg Arg Leu Leu Arg Phe Ser Ser Gln Ile His Asn Asn Gly Gln  
                     595                      600                      605  
 Ser Asp Phe Arg Pro Lys Asn Gly Arg His Ala Trp Ile Trp His Asp  
                     610                      615                      620  
 Cys His Arg His Tyr His Ser Met Glu Val Phe Thr His Tyr Asp Leu  
 625                      630                      635                      640  
 Leu Asn Leu Asn Gly Thr Lys Val Ala Glu Gly His Lys Ala Ser Phe  
                     645                      650                      655  
 Cys Leu Glu Asp Thr Glu Cys Glu Gly Asp Ile Gln Lys Asn Tyr Glu  
                     660                      665                      670  
 Cys Ala Asn Phe Gly Asp Gln Gly Ile Thr Met Gly Cys Trp Asp Met  
                     675                      680                      685  
 Tyr Arg His Asp Ile Asp Cys Gln Trp Val Asp Ile Thr Asp Val Pro  
                     690                      695                      700  
 Pro Gly Asp Tyr Leu Phe Gln Val Val Ile Asn Pro Asn Phe Glu Val  
 705                      710                      715                      720  
 Ala Glu Ser Asp Tyr Ser Asn Asn Ile Met Lys Cys Arg Ser Arg Tyr  
                     725                      730                      735  
 Asp Gly His Arg Ile Trp Met Tyr Asn Cys His Ile Gly Gly Ser Phe  
                     740                      745                      750  
 Ser Glu Glu Thr Glu Lys Lys Phe Glu His Phe Ser Gly Leu Leu Asn  
                     755                      760                      765  
 Asn Gln Leu Ser Pro Gln  
 770

<210> 123

<211> 297  
 <212> PRT  
 <213> Homo sapiens

<400> 123

Met Glu Asp Tyr Thr Lys Ile Glu Lys Ile Gly Glu Gly Thr Tyr Gly  
 1 5 10 15

Val Val Tyr Lys Gly Arg His Lys Thr Thr Gly Gln Val Val Ala Met  
 20 25 30

Lys Lys Ile Arg Leu Glu Ser Glu Glu Glu Gly Val Pro Ser Thr Ala  
 35 40 45

Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Arg His Pro Asn Ile Val  
 50 55 60

Ser Leu Gln Asp Val Leu Met Gln Asp Ser Arg Leu Tyr Leu Ile Phe  
 65 70 75 80

Glu Phe Leu Ser Met Asp Leu Lys Lys Tyr Leu Asp Ser Ile Pro Pro  
 85 90 95

Gly Gln Tyr Met Asp Ser Ser Leu Val Lys Ser Tyr Leu Tyr Gln Ile  
 100 105 110

Leu Gln Gly Ile Val Phe Cys His Ser Arg Arg Val Leu His Arg Asp  
 115 120 125

Leu Lys Pro Gln Asn Leu Leu Ile Asp Asp Lys Gly Thr Ile Lys Leu  
 130 135 140

Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Ile Pro Ile Arg Val Tyr  
 145 150 155 160

Thr His Glu Val Val Thr Leu Trp Tyr Arg Ser Pro Glu Val Leu Leu  
 165 170 175

Gly Ser Ala Arg Tyr Ser Thr Pro Val Asp Ile Trp Ser Ile Gly Thr  
 180 185 190

Ile Phe Ala Glu Leu Ala Thr Lys Lys Pro Leu Phe His Gly Asp Ser  
 195 200 205

Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Ala Leu Gly Thr Pro Asn  
 210 215 220

Asn Glu Val Trp Pro Glu Val Glu Ser Leu Gln Asp Tyr Lys Asn Thr  
 225 230 235 240

Phe Pro Lys Trp Lys Pro Gly Ser Leu Ala Ser His Val Lys Asn Leu  
 245 250 255

Asp Glu Asn Gly Leu Asp Leu Leu Ser Lys Met Leu Ile Tyr Asp Pro  
 260 265 270

Ala Lys Arg Ile Ser Gly Lys Met Ala Leu Asn His Pro Tyr Phe Asn  
 275 280 285

Asp Leu Asp Asn Gln Ile Lys Lys Met  
 290 295

<210> 124  
 <211> 145  
 <212> PRT  
 <213> Homo sapiens

<400> 124

Met Arg Gln Ala Gly Glu Val Thr Phe Ala Asp Ala His Arg Pro Lys  
 1 5 10 15

Leu Asn Glu Gly Val Val Glu Phe Ala Ser Tyr Gly Asp Leu Lys Asn  
 20 25 30

Ala Ile Glu Lys Leu Ser Gly Lys Glu Ile Asn Gly Arg Lys Ile Lys  
 35 40 45

Leu Ile Glu Gly Ser Lys Arg His Ser Arg Ser Arg Ser Arg Ser Arg  
 50 55 60

Ser Arg Thr Arg Ser Ser Ser Arg Ser Arg Ser Arg Ser Arg Ser Arg  
 65 70 75 80

Ser Arg Lys Ser Tyr Ser Arg Ser Arg Ser Arg Ser Arg Ser Arg Ser  
 85 90 95

Arg Ser Lys Ser Arg Ser Val Ser Arg Ser Pro Val Pro Glu Lys Ser  
 100 105 110

Gln Lys Arg Gly Ser Ser Ser Arg Ser Lys Ser Pro Ala Ser Val Asp  
 115 120 125

Arg Gln Arg Ser Arg Ser Arg Ser Arg Ser Val Asp Ser Gly  
 130 135 140

Asn  
 145

<210> 125  
 <211> 814  
 <212> PRT  
 <213> Homo sapiens

<400> 125

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Met Gln Asp Ala Glu Asn Val Ala Val Pro Glu Ala Ala Glu Glu Arg
1      5      10      15

Ala Glu Pro Gly Gln Gln Gln Pro Ala Ala Glu Pro Pro Pro Ala Glu
20      25      30

Gly Leu Leu Arg Pro Ala Gly Pro Gly Ala Pro Glu Ala Ala Gly Thr
35      40      45

Glu Ala Ser Ser Glu Glu Val Gly Ile Ala Glu Ala Gly Pro Glu Pro
50      55      60

Glu Val Arg Thr Glu Pro Ala Ala Glu Ala Glu Ala Ala Ser Gly Pro
65      70      75      80

Ser Glu Ser Pro Ser Pro Pro Ala Ala Glu Glu Leu Pro Gly Ser His
85      90      95

Ala Glu Pro Pro Val Pro Ala Gln Gly Glu Ala Pro Gly Glu Gln Ala
100     105     110

Arg Asp Glu Arg Ser Asp Ser Arg Ala Gln Ala Val Ser Glu Asp Ala
115     120     125

Gly Gly Asn Glu Gly Arg Ala Ala Glu Ala Glu Pro Arg Ala Leu Glu
130     135     140

Asn Gly Asp Ala Asp Glu Pro Ser Phe Ser Asp Pro Glu Asp Phe Val
145     150     155     160

Asp Asp Val Ser Glu Glu Glu Leu Leu Gly Asp Val Leu Lys Asp Arg
165     170     175

Pro Gln Glu Ala Asp Gly Ile Asp Ser Val Ile Val Val Asp Asn Val
180     185     190

Pro Gln Val Gly Pro Asp Arg Leu Glu Lys Leu Lys Asn Val Ile His
195     200     205

Lys Ile Phe Ser Lys Phe Gly Lys Ile Thr Asn Asp Phe Tyr Pro Glu
210     215     220

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Glu Asp Gly Lys Thr Lys Gly Tyr Ile Phe Leu Glu Tyr Ala Ser Pro  
 225 230 235 240  
 Ala His Ala Val Asp Ala Val Lys Asn Ala Asp Gly Tyr Lys Leu Asp  
 245 250 255  
 Lys Gln His Thr Phe Arg Val Asn Leu Phe Thr Asp Phe Asp Lys Tyr  
 260 265 270  
 Met Thr Ile Ser Asp Glu Trp Asp Ile Pro Glu Lys Gln Pro Phe Lys  
 275 280 285  
 Asp Leu Gly Asn Leu Arg Tyr Trp Leu Glu Glu Ala Glu Cys Arg Asp  
 290 295 300  
 Gln Tyr Ser Val Ile Phe Glu Ser Gly Asp Arg Thr Ser Ile Phe Trp  
 305 310 315 320  
 Asn Asp Val Lys Asp Pro Val Ser Ile Glu Glu Arg Ala Arg Trp Thr  
 325 330 335  
 Glu Thr Tyr Val Arg Trp Ser Pro Lys Gly Thr Tyr Leu Ala Thr Phe  
 340 345 350  
 His Gln Arg Gly Ile Ala Leu Trp Gly Gly Glu Lys Phe Lys Gln Ile  
 355 360 365  
 Gln Arg Phe Ser His Gln Gly Val Gln Leu Ile Asp Phe Ser Pro Cys  
 370 375 380  
 Glu Arg Tyr Leu Val Thr Phe Ser Pro Leu Met Asp Thr Gln Asp Asp  
 385 390 395 400  
 Pro Gln Ala Ile Ile Ile Trp Asp Ile Leu Thr Gly His Lys Lys Arg  
 405 410 415  
 Gly Phe His Cys Glu Ser Ser Ala His Trp Pro Ile Phe Lys Trp Ser  
 420 425 430  
 His Asp Gly Lys Phe Phe Ala Arg Met Thr Leu Asp Thr Leu Ser Ile  
 435 440 445  
 Tyr Glu Thr Pro Ser Met Gly Leu Leu Asp Lys Lys Ser Leu Lys Ile  
 450 455 460  
 Ser Gly Ile Lys Asp Phe Ser Trp Ser Pro Gly Gly Asn Ile Ile Ala  
 465 470 475 480

Phe Trp Val Pro Glu Asp Lys Asp Ile Pro Ala Arg Val Thr Leu Met  
 485 490 495

Gln Leu Pro Thr Arg Gln Glu Ile Arg Val Arg Asn Leu Phe Asn Val  
 500 505 510

Val Asp Cys Lys Leu His Trp Gln Lys Asn Gly Asp Tyr Leu Cys Val  
 515 520 525

Lys Val Asp Arg Thr Pro Lys Gly Thr Gln Gly Val Val Thr Asn Phe  
 530 535 540

Glu Ile Phe Arg Met Arg Glu Lys Gln Val Pro Val Asp Val Val Glu  
 545 550 555 560

Met Lys Glu Thr Ile Ile Ala Phe Ala Trp Glu Pro Asn Gly Ser Lys  
 565 570 575

Phe Ala Val Leu His Gly Glu Ala Pro Arg Ile Ser Val Ser Phe Tyr  
 580 585 590

His Val Lys Asn Asn Gly Lys Ile Glu Leu Ile Lys Met Phe Asp Lys  
 595 600 605

Gln Gln Ala Asn Thr Ile Phe Trp Ser Pro Gln Gly Gln Phe Val Val  
 610 615 620

Leu Ala Gly Leu Arg Ser Met Asn Gly Ala Leu Ala Phe Val Asp Thr  
 625 630 635 640

Ser Asp Cys Thr Val Met Asn Ile Ala Glu His Tyr Met Ala Ser Asp  
 645 650 655

Val Glu Trp Asp Pro Thr Gly Arg Tyr Val Val Thr Ser Val Ser Trp  
 660 665 670

Trp Ser His Lys Val Asp Asn Ala Tyr Trp Leu Trp Thr Phe Gln Gly  
 675 680 685

Arg Leu Leu Gln Lys Asn Asn Lys Asp Arg Phe Cys Gln Leu Leu Trp  
 690 695 700

Arg Pro Arg Pro Pro Thr Leu Leu Ser Gln Glu Gln Ile Lys Gln Ile  
 705 710 715 720

Lys Lys Asp Leu Lys Lys Tyr Ser Lys Ile Phe Glu Gln Lys Asp Arg  
 725 730 735

Leu Ser Gln Ser Lys Ala Ser Lys Glu Leu Val Glu Arg Arg Arg Thr  
740 745 750

Met Met Glu Asp Phe Arg Lys Tyr Arg Lys Met Ala Gln Glu Leu Tyr  
755 760 765

Met Glu Gln Lys Asn Glu Arg Leu Glu Leu Arg Gly Gly Val Asp Thr  
770 775 780

Asp Glu Leu Asp Ser Asn Val Asp Asp Trp Glu Glu Glu Thr Ile Glu  
785 790 795 800

Phe Phe Val Thr Glu Glu Ile Ile Pro Leu Gly Asn Gln Glu  
805 810

<210> 126  
<211> 197  
<212> PRT  
<213> Homo sapiens

<400> 126

Met Pro Ala Pro Ser Met Asp Cys Asp Val Ser Thr Leu Val Ala Cys  
1 5 10 15

Val Val Asp Val Glu Val Phe Thr Asn Gln Glu Val Lys Glu Lys Phe  
20 25 30

Gly Gly Leu Phe Arg Thr Tyr Asp Asp Cys Val Thr Phe Gln Leu Phe  
35 40 45

Lys Ser Phe Arg Arg Val Arg Ile Asn Phe Ser Asn Pro Lys Ser Ala  
50 55 60

Ala Arg Ala Arg Ile Glu Leu His Glu Thr Gln Phe Arg Gly Lys Lys  
65 70 75 80

Leu Lys Leu Tyr Phe Ala Gln Val Gln Thr Pro Glu Thr Asp Gly Asp  
85 90 95

Lys Leu His Leu Ala Pro Pro Gln Pro Ala Lys Gln Phe Leu Ile Ser  
100 105 110

Pro Pro Ser Ser Pro Pro Val Ser Trp Gln Pro Ile Asn Asp Ala Thr  
115 120 125

Pro Val Leu Asn Tyr Asp Leu Leu Tyr Ala Val Ala Lys Leu Gly Pro  
130 135 140

Gly Glu Lys Tyr Glu Leu His Ala Gly Thr Glu Ser Thr Pro Ser Val

145                      150                      155                      160  
 Val Val His Val Cys Asp Ser Asp Ile Glu Glu Glu Glu Asp Pro Lys  
                                  165                                   170                                   175

Thr Ser Pro Lys Pro Lys Ile Ile Gln Thr Arg Arg Pro Gly Leu Pro  
                                  180                                   185                                   190

Pro Ser Val Ser Asn  
                                  195

<210> 127  
 <211> 1390  
 <212> PRT  
 <213> Homo sapiens

<400> 127

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Phe  
 1                                   5                                   10                                   15

Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys  
                                  20                                   25                                   30

Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala  
                                  35                                   40                                   45

Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu  
                                  50                                   55                                   60

Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys  
 65                                   70                                   75                                   80

Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe  
                                  85                                   90                                   95

Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp  
                                  100                                   105                                   110

Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp  
                                  115                                   120                                   125

Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His  
                                  130                                   135                                   140

Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys  
 145                                   150                                   155                                   160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val  
                                  165                                   170                                   175



Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe  
 180 185 190  
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp  
 195 200 205  
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp  
 210 215 220  
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu  
 225 230 235 240  
 Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn  
 245 250 255  
 Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln  
 260 265 270  
 Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu  
 275 280 285  
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg  
 290 295 300  
 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala  
 305 310 315 320  
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser  
 325 330 335  
 Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp  
 340 345 350  
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys  
 355 360 365  
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg  
 370 375 380  
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg  
 385 390 395 400  
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr  
 405 410 415  
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly  
 420 425 430

Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly  
435 440 445

Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln  
450 455 460

Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu  
465 470 475 480

Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu  
485 490 495

Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys  
500 505 510

Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln  
515 520 525

Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys  
530 535 540

Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile  
545 550 555 560

Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu  
565 570 575

Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg  
580 585 590

Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu  
595 600 605

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys  
610 615 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile  
625 630 635 640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp  
645 650 655

Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly  
660 665 670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg  
675 680 685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn  
 690 695 700  
 Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe  
 705 710 715 720  
 Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe  
 725 730 735  
 Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser  
 740 745 750  
 Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu Asn  
 755 760 765  
 Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg  
 770 775 780  
 Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys  
 785 790 795 800  
 Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys  
 805 810 815  
 Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp  
 820 825 830  
 Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val  
 835 840 845  
 Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp  
 850 855 860  
 Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys  
 865 870 875 880  
 Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val  
 885 890 895  
 Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys  
 900 905 910  
 Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp  
 915 920 925  
 Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser Thr Ala  
 930 935 940

Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg Lys Gln  
 945 950 955 960  
 Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His  
 965 970 975  
 Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr  
 980 985 990  
 Thr Glu Met Val Ser Asn Glu Ser Val Asp Tyr Arg Ala Thr Phe Pi  
 995 1000 1005  
 Glu Asp Gln Phe Pro Asn Ser Ser Gln Asn Gly Ser Cys Arg Gln  
 1010 1015 1020  
 Val Gln Tyr Pro Leu Thr Asp Met Ser Pro Ile Leu Thr Ser Gly  
 1025 1030 1035  
 Asp Ser Asp Ile Ser Ser Pro Leu Leu Gln Asn Thr Val His Ile  
 1040 1045 1050  
 Asp Leu Ser Ala Leu Asn Pro Glu Leu Val Gln Ala Val Gln His  
 1055 1060 1065  
 Val Val Ile Gly Pro Ser Ser Leu Ile Val His Phe Asn Glu Val  
 1070 1075 1080  
 Ile Gly Arg Gly His Phe Gly Cys Val Tyr His Gly Thr Leu Leu  
 1085 1090 1095  
 Asp Asn Asp Gly Lys Lys Ile His Cys Ala Val Lys Ser Leu Asn  
 1100 1105 1110  
 Arg Ile Thr Asp Ile Gly Glu Val Ser Gln Phe Leu Thr Glu Gly  
 1115 1120 1125  
 Ile Ile Met Lys Asp Phe Ser His Pro Asn Val Leu Ser Leu Leu  
 1130 1135 1140  
 Gly Ile Cys Leu Arg Ser Glu Gly Ser Pro Leu Val Val Leu Pro  
 1145 1150 1155  
 Tyr Met Lys His Gly Asp Leu Arg Asn Phe Ile Arg Asn Glu Thr  
 1160 1165 1170  
 His Asn Pro Thr Val Lys Asp Leu Ile Gly Phe Gly Leu Gln Val  
 1175 1180 1185

Ala Lys Gly Met Lys Tyr Leu Ala Ser Lys Lys Phe Val His Arg  
 1190 1195 1200  
 Asp Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys Phe Thr Val  
 1205 1210 1215  
 Lys Val Ala Asp Phe Gly Leu Ala Arg Asp Met Tyr Asp Lys Glu  
 1220 1225 1230  
 Tyr Tyr Ser Val His Asn Lys Thr Gly Ala Lys Leu Pro Val Lys  
 1235 1240 1245  
 Trp Met Ala Leu Glu Ser Leu Gln Thr Gln Lys Phe Thr Thr Lys  
 1250 1255 1260  
 Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp Glu Leu Met Thr  
 1265 1270 1275  
 Arg Gly Ala Pro Pro Tyr Pro Asp Val Asn Thr Phe Asp Ile Thr  
 1280 1285 1290  
 Val Tyr Leu Leu Gln Gly Arg Arg Leu Leu Gln Pro Glu Tyr Cys  
 1295 1300 1305  
 Pro Asp Pro Leu Tyr Glu Val Met Leu Lys Cys Trp His Pro Lys  
 1310 1315 1320  
 Ala Glu Met Arg Pro Ser Phe Ser Glu Leu Val Ser Arg Ile Ser  
 1325 1330 1335  
 Ala Ile Phe Ser Thr Phe Ile Gly Glu His Tyr Val His Val Asn  
 1340 1345 1350  
 Ala Thr Tyr Val Asn Val Lys Cys Val Ala Pro Tyr Pro Ser Leu  
 1355 1360 1365  
 Leu Ser Ser Glu Asp Asn Ala Asp Asp Glu Val Asp Thr Arg Pro  
 1370 1375 1380  
 Ala Ser Phe Trp Glu Thr Ser  
 1385 1390

<210> 128  
 <211> 417  
 <212> PRT  
 <213> Homo sapiens  
 <400> 128

Ser Ile Glu Ile Pro Ala Gly Leu Thr Glu Leu Leu Gln Gly Phe Thr  
 1 5 10 15  
 Val Glu Val Leu Arg His Gln Pro Ala Asp Leu Leu Glu Phe Ala Leu  
 20 25 30  
 Gln His Phe Thr Arg Leu Gln Gln Glu Asn Glu Arg Lys Gly Thr Ala  
 35 40 45  
 Arg Phe Gly His Glu Gly Arg Thr Trp Gly Asp Leu Gly Ala Ala Ala  
 50 55 60  
 Gly Gly Gly Thr Pro Ser Lys Gly Val Asn Phe Ala Glu Glu Pro Met  
 65 70 75 80  
 Gln Ser Asp Ser Glu Asp Gly Glu Glu Glu Glu Ala Ala Pro Ala Asp  
 85 90 95  
 Ala Gly Ala Phe Asn Ala Pro Val Ile Asn Arg Phe Thr Arg Arg Ala  
 100 105 110  
 Ser Val Cys Ala Glu Ala Tyr Asn Pro Asp Glu Glu Glu Asp Asp Ala  
 115 120 125  
 Glu Ser Arg Ile Ile His Pro Lys Thr Asp Asp Gln Arg Asn Arg Leu  
 130 135 140  
 Gln Glu Ala Cys Lys Asp Ile Leu Leu Phe Lys Asn Leu Asp Pro Glu  
 145 150 155 160  
 Gln Met Ser Gln Val Leu Asp Ala Met Phe Glu Lys Leu Val Lys Asp  
 165 170 175  
 Gly Glu His Val Ile Asp Gln Gly Asp Asp Gly Asp Asn Phe Tyr Val  
 180 185 190  
 Ile Asp Arg Gly Thr Phe Asp Ile Tyr Val Lys Cys Asp Gly Val Gly  
 195 200 205  
 Arg Cys Val Gly Asn Tyr Asp Asn Arg Gly Ser Phe Gly Glu Leu Ala  
 210 215 220  
 Leu Met Tyr Asn Thr Pro Arg Ala Ala Thr Ile Thr Ala Thr Ser Pro  
 225 230 235 240  
 Gly Ala Leu Trp Gly Leu Asp Arg Val Thr Phe Arg Arg Ile Ile Val  
 245 250 255

Lys Asn Asn Ala Lys Lys Arg Lys Met Tyr Glu Ser Phe Ile Glu Ser  
260 265 270

Leu Pro Phe Leu Lys Ser Leu Glu Phe Ser Glu Arg Leu Lys Val Val  
275 280 285

Asp Val Ile Gly Thr Lys Val Tyr Asn Asp Gly Glu Gln Ile Ile Ala  
290 295 300

Gln Gly Asp Ser Ala Asp Ser Phe Phe Ile Val Glu Ser Gly Glu Val  
305 310 315 320

Lys Ile Thr Met Lys Arg Lys Gly Lys Ser Glu Val Glu Glu Asn Gly  
325 330 335

Ala Val Glu Met Pro Arg Cys Ser Arg Gly Gln Tyr Phe Gly Glu Leu  
340 345 350

Ala Leu Val Thr Asn Lys Pro Arg Ala Ala Ser Ala His Ala Ile Gly  
355 360 365

Thr Val Lys Cys Leu Ala Met Asp Val Gln Ala Phe Glu Arg Leu Leu  
370 375 380

Gly Pro Cys Met Glu Ile Met Lys Arg Asn Ile Ala Thr Tyr Glu Glu  
385 390 395 400

Gln Leu Val Ala Leu Phe Gly Thr Asn Met Asp Ile Val Glu Pro Thr  
405 410 415

Ala

<210> 129  
<211> 425  
<212> PRT  
<213> Homo sapiens

<400> 129

Met Gly Pro Arg Arg Leu Leu Leu Val Ala Ala Cys Phe Ser Leu Cys  
1 5 10 15

Gly Pro Leu Leu Ser Ala Arg Thr Arg Ala Arg Arg Pro Glu Ser Lys  
20 25 30

Ala Thr Asn Ala Thr Leu Asp Pro Arg Ser Phe Leu Leu Arg Asn Pro  
35 40 45

Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Lys Asn Glu Ser  
 50 55 60  
 Gly Leu Thr Glu Tyr Arg Leu Val Ser Ile Asn Lys Ser Ser Pro Leu  
 65 70 75 80  
 Gln Lys Gln Leu Pro Ala Phe Ile Ser Glu Asp Ala Ser Gly Tyr Leu  
 85 90 95  
 Thr Ser Ser Trp Leu Thr Leu Phe Val Pro Ser Val Tyr Thr Gly Val  
 100 105 110  
 Phe Val Val Ser Leu Pro Leu Asn Ile Met Ala Ile Val Val Phe Ile  
 115 120 125  
 Leu Lys Met Lys Val Lys Lys Pro Ala Val Val Tyr Met Leu His Leu  
 130 135 140  
 Ala Thr Ala Asp Val Leu Phe Val Ser Val Leu Pro Phe Lys Ile Ser  
 145 150 155 160  
 Tyr Tyr Phe Ser Gly Ser Asp Trp Gln Phe Gly Ser Glu Leu Cys Arg  
 165 170 175  
 Phe Val Thr Ala Ala Phe Tyr Cys Asn Met Tyr Ala Ser Ile Leu Leu  
 180 185 190  
 Met Thr Val Ile Ser Ile Asp Arg Phe Leu Ala Val Val Tyr Pro Met  
 195 200 205  
 Gln Ser Leu Ser Trp Arg Thr Leu Gly Arg Ala Ser Phe Thr Cys Leu  
 210 215 220  
 Ala Ile Trp Ala Leu Ala Ile Ala Gly Val Val Pro Leu Leu Leu Lys  
 225 230 235 240  
 Glu Gln Thr Ile Gln Val Pro Gly Leu Asn Ile Thr Thr Cys His Asp  
 245 250 255  
 Val Leu Asn Glu Thr Leu Leu Glu Gly Tyr Tyr Ala Tyr Tyr Phe Ser  
 260 265 270  
 Ala Phe Ser Ala Val Phe Phe Phe Val Pro Leu Ile Ile Ser Thr Val  
 275 280 285  
 Cys Tyr Val Ser Ile Ile Arg Cys Leu Ser Ser Ser Ala Val Ala Asn  
 290 295 300



Arg Ser Lys Lys Ser Arg Ala Leu Phe Leu Ser Ala Ala Val Phe Cys  
305 310 315 320

Ile Phe Ile Ile Cys Phe Gly Pro Thr Asn Val Leu Leu Ile Ala His  
325 330 335

Tyr Ser Phe Leu Ser His Thr Ser Thr Thr Glu Ala Ala Tyr Phe Ala  
340 345 350

Tyr Leu Leu Cys Val Cys Val Ser Ser Ile Ser Cys Cys Ile Asp Pro  
355 360 365

Leu Ile Tyr Tyr Tyr Ala Ser Ser Glu Cys Gln Arg Tyr Val Tyr Ser  
370 375 380

Ile Leu Cys Cys Lys Glu Ser Ser Asp Pro Ser Ser Tyr Asn Ser Ser  
385 390 395 400

Gly Gln Leu Met Ala Ser Lys Met Asp Thr Cys Ser Ser Asn Leu Asn  
405 410 415

Asn Ser Ile Tyr Lys Lys Leu Leu Thr  
420 425

<210> 130  
<211> 364  
<212> PRT  
<213> Homo sapiens

<400> 130

Met Ala Ala Ile Ser Thr Ser Ile Pro Val Ile Ser Gln Pro Gln Phe  
1 5 10 15

Thr Ala Met Asn Glu Pro Gln Cys Phe Tyr Asn Glu Ser Ile Ala Phe  
20 25 30

Phe Tyr Asn Arg Ser Gly Lys His Leu Ala Thr Glu Trp Asn Thr Val  
35 40 45

Ser Lys Leu Val Met Gly Leu Gly Ile Thr Val Cys Ile Phe Ile Met  
50 55 60

Leu Ala Asn Leu Leu Val Met Val Ala Ile Tyr Val Asn Arg Arg Phe  
65 70 75 80

His Phe Pro Ile Tyr Tyr Leu Met Ala Asn Leu Ala Ala Ala Asp Phe  
85 90 95

Phe Ala Gly Leu Ala Tyr Phe Tyr Leu Met Phe Asn Thr Gly Pro Asn

100	105	110
Thr Arg Arg Leu Thr Val Ser	Thr Trp Leu Leu Arg	Gln Gly Leu Ile
115	120	125
Asp Thr Ser Leu Thr Ala Ser Val Ala Asn Leu Leu Ala Ile Ala Ile		
130	135	140
Glu Arg His Ile Thr Val Phe Arg Met Gln Leu His Thr Arg Met Ser		
145	150	155
Asn Arg Arg Val Val Val Val Ile Val Val Ile Trp Thr Met Ala Ile		
165	170	175
Val Met Gly Ala Ile Pro Ser Val Gly Trp Asn Cys Ile Cys Asp Ile		
180	185	190
Glu Asn Cys Ser Asn Met Ala Pro Leu Tyr Ser Asp Ser Tyr Leu Val		
195	200	205
Phe Trp Ala Ile Phe Asn Leu Val Thr Phe Val Val Met Val Val Leu		
210	215	220
Tyr Ala His Ile Phe Gly Tyr Val Arg Gln Arg Thr Met Arg Met Ser		
225	230	235
Arg His Ser Ser Gly Pro Arg Arg Asn Arg Asp Thr Met Met Ser Leu		
245	250	255
Leu Lys Thr Val Val Ile Val Leu Gly Ala Phe Ile Ile Cys Trp Thr		
260	265	270
Pro Gly Leu Val Leu Leu Leu Leu Asp Val Cys Cys Pro Gln Cys Asp		
275	280	285
Val Leu Ala Tyr Glu Lys Phe Phe Leu Leu Leu Ala Glu Phe Asn Ser		
290	295	300
Ala Met Asn Pro Ile Ile Tyr Ser Tyr Arg Asp Lys Glu Met Ser Ala		
305	310	315
Thr Phe Arg Gln Ile Leu Cys Cys Gln Arg Ser Glu Asn Pro Thr Gly		
325	330	335
Pro Thr Glu Gly Ser Asp Arg Ser Ala Ser Ser Leu Asn His Thr Ile		
340	345	350
Leu Ala Gly Val His Ser Asn Asp His Ser Val Val		

355

360

<210> 131  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<400> 131

Met Ala His Lys Gln Ile Tyr Tyr Ser Asp Lys Tyr Phe Asp Glu His  
 1 5 10 15

Tyr Glu Tyr Arg His Val Met Leu Pro Arg Glu Leu Ser Lys Gln Val  
 20 25 30

Pro Lys Thr His Leu Met Ser Glu Glu Glu Trp Arg Arg Leu Gly Val  
 35 40 45

Gln Gln Ser Leu Gly Trp Val His Tyr Met Ile His Glu Pro Glu Pro  
 50 55 60

His Ile Leu Leu Phe Arg Arg Pro Leu Pro Lys Asp Gln Gln Lys  
 65 70 75

<210> 132  
 <211> 234  
 <212> PRT  
 <213> Homo sapiens

<400> 132

Met Asn Ser Gly Ala Met Arg Ile His Ser Lys Gly His Phe Gln Gly  
 1 5 10 15

Gly Ile Gln Val Lys Asn Glu Lys Asn Arg Pro Ser Leu Lys Ser Leu  
 20 25 30

Lys Thr Asp Asn Arg Pro Glu Lys Ser Lys Cys Lys Pro Leu Trp Gly  
 35 40 45

Lys Val Phe Tyr Leu Asp Leu Pro Ser Val Thr Ile Ser Glu Lys Leu  
 50 55 60

Gln Lys Asp Ile Lys Asp Leu Gly Gly Arg Val Glu Glu Phe Leu Ser  
 65 70 75 80

Lys Asp Ile Ser Tyr Leu Ile Ser Asn Lys Lys Glu Ala Lys Phe Ala  
 85 90 95

Gln Thr Leu Gly Arg Ile Ser Pro Val Pro Ser Pro Glu Ser Ala Tyr  
 100 105 110

Thr Ala Glu Thr Thr Ser Pro His Pro Ser His Asp Gly Ser Ser Phe  
 115 120 125

Lys Ser Pro Asp Thr Val Cys Leu Ser Arg Gly Lys Leu Leu Val Glu  
 130 135 140

Lys Ala Ile Lys Asp His Asp Phe Ile Pro Ser Asn Ser Ile Leu Ser  
 145 150 155 160

Asn Ala Leu Ser Trp Gly Val Lys Ile Leu His Ile Asp Asp Ile Arg  
 165 170 175

Tyr Tyr Ile Glu Gln Lys Lys Lys Glu Leu Tyr Leu Leu Lys Lys Ser  
 180 185 190

Ser Thr Ser Val Arg Asp Gly Gly Lys Arg Val Gly Ser Gly Ala Gln  
 195 200 205

Lys Thr Arg Thr Gly Arg Leu Lys Lys Pro Phe Val Lys Val Glu Asp  
 210 215 220

Met Ser Gln Ser Pro Ala Val His Leu Met  
 225 230

<210> 133  
 <211> 403  
 <212> PRT  
 <213> Homo sapiens

<400> 133

Met Gln Arg Ala Val Ser Val Val Ala Arg Leu Gly Phe Arg Leu Gln  
 1 5 10 15

Ala Phe Pro Pro Ala Leu Cys Arg Pro Leu Ser Cys Ala Gln Glu Val  
 20 25 30

Leu Arg Arg Thr Pro Leu Tyr Asp Phe His Leu Ala His Gly Gly Lys  
 35 40 45

Met Val Ala Phe Ala Gly Trp Ser Leu Pro Val Gln Tyr Arg Asp Ser  
 50 55 60

His Thr Asp Ser His Leu His Thr Arg Gln His Cys Ser Leu Phe Asp  
 65 70 75 80

Val Ser His Met Leu Gln Thr Lys Ile Leu Gly Ser Asp Arg Val Lys  
 85 90 95

Leu Met Glu Ser Leu Val Val Gly Asp Ile Ala Glu Leu Arg Pro Asn  
 100 105 110  
 Gln Gly Thr Leu Ser Leu Phe Thr Asn Glu Ala Gly Gly Ile Leu Asp  
 115 120 125  
 Asp Leu Ile Val Thr Asn Thr Ser Glu Gly His Leu Tyr Val Val Ser  
 130 135 140  
 Asn Ala Gly Cys Trp Glu Lys Asp Leu Ala Leu Met Gln Asp Lys Val  
 145 150 155 160  
 Arg Glu Leu Gln Asn Gln Gly Arg Asp Val Gly Leu Glu Val Leu Asp  
 165 170 175  
 Asn Ala Leu Leu Ala Leu Gln Gly Pro Thr Ala Ala Gln Val Leu Gln  
 180 185 190  
 Ala Gly Val Ala Asp Asp Leu Arg Lys Leu Pro Phe Met Thr Ser Ala  
 195 200 205  
 Val Met Glu Val Phe Gly Val Ser Gly Cys Arg Val Thr Arg Cys Gly  
 210 215 220  
 Tyr Thr Gly Glu Asp Gly Val Glu Ile Ser Val Pro Val Ala Gly Ala  
 225 230 235 240  
 Val His Leu Ala Thr Ala Ile Leu Lys Asn Pro Glu Val Lys Leu Ala  
 245 250 255  
 Gly Leu Ala Ala Arg Asp Ser Leu Arg Leu Glu Ala Gly Leu Cys Leu  
 260 265 270  
 Tyr Gly Asn Asp Ile Asp Glu His Thr Thr Pro Val Glu Gly Ser Leu  
 275 280 285  
 Ser Trp Thr Leu Gly Lys Arg Arg Arg Ala Ala Met Asp Phe Pro Gly  
 290 295 300  
 Ala Lys Val Ile Val Pro Gln Leu Lys Gly Arg Val Gln Arg Arg Arg  
 305 310 315 320  
 Val Gly Leu Met Cys Glu Gly Ala Pro Met Arg Ala His Ser Pro Ile  
 325 330 335  
 Leu Asn Met Glu Gly Thr Lys Ile Gly Thr Val Thr Ser Gly Cys Pro  
 340 345 350

Ser Pro Ser Leu Lys Lys Asn Val Ala Met Gly Tyr Val Pro Cys Glu  
355 360 365

Tyr Ser Arg Pro Gly Thr Met Leu Leu Val Glu Val Arg Arg Lys Gln  
370 375 380

Gln Met Ala Val Val Ser Lys Met Pro Phe Val Pro Thr Asn Tyr Tyr  
385 390 395 400

Thr Leu Lys

<210> 134  
<211> 526  
<212> PRT  
<213> Homo sapiens

<400> 134

Met Asp Val Arg Phe Tyr Pro Pro Val Ala Gln Pro Ala Ala Ala Pro  
1 5 10 15

Asp Ala Pro Cys Leu Gly Pro Ser Pro Cys Leu Asp Pro Tyr Tyr Cys  
20 25 30

Asn Lys Phe Asp Gly Glu Asn Met Tyr Met Ser Met Thr Glu Pro Ser  
35 40 45

Gln Asp Tyr Val Pro Ala Ser Gln Ser Tyr Pro Gly Pro Ser Leu Glu  
50 55 60

Ser Glu Asp Phe Asn Ile Pro Pro Ile Thr Pro Pro Ser Leu Pro Asp  
65 70 75 80

His Ser Leu Val His Leu Asn Glu Val Glu Ser Gly Tyr His Ser Leu  
85 90 95

Cys His Pro Met Asn His Asn Gly Leu Leu Pro Phe His Pro Gln Asn  
100 105 110

Met Asp Leu Pro Glu Ile Thr Val Ser Asn Met Leu Gly Gln Asp Gly  
115 120 125

Thr Leu Leu Ser Asn Ser Ile Ser Val Met Pro Asp Ile Arg Asn Pro  
130 135 140

Glu Gly Thr Gln Tyr Ser Ser His Pro Gln Met Ala Ala Met Arg Pro  
145 150 155 160

Arg Gly Gln Pro Ala Asp Ile Arg Gln Gln Pro Gly Met Met Pro His

165										170					175				
Gly	Gln	Leu	Thr	Thr	Ile	Asn	Gln	Ser	Gln	Leu	Ser	Ala	Gln	Leu	Gly				
			180					185					190						
Leu	Asn	Met	Gly	Gly	Ser	Asn	Val	Pro	His	Asn	Ser	Pro	Ser	Pro	Pro				
		195					200					205							
Gly	Ser	Lys	Ser	Ala	Thr	Pro	Ser	Pro	Ser	Ser	Ser	Val	His	Glu	Asp				
	210					215					220								
Glu	Gly	Asp	Asp	Thr	Ser	Lys	Ile	Asn	Gly	Gly	Glu	Lys	Arg	Pro	Ala				
225					230				235					240					
Ser	Asp	Met	Gly	Lys	Lys	Pro	Lys	Thr	Pro	Lys	Lys	Lys	Lys	Lys	Lys				
				245					250					255					
Asp	Pro	Asn	Glu	Pro	Gln	Lys	Pro	Val	Ser	Ala	Tyr	Ala	Leu	Phe	Phe				
			260					265					270						
Arg	Asp	Thr	Gln	Ala	Ala	Ile	Lys	Gly	Gln	Asn	Pro	Asn	Ala	Thr	Phe				
		275					280					285							
Gly	Glu	Val	Ser	Lys	Ile	Val	Ala	Ser	Met	Trp	Asp	Gly	Leu	Gly	Glu				
	290					295					300								
Glu	Gln	Lys	Gln	Val	Tyr	Lys	Lys	Lys	Thr	Glu	Ala	Ala	Lys	Lys	Glu				
305					310					315					320				
Tyr	Leu	Lys	Gln	Leu	Ala	Ala	Tyr	Arg	Ala	Ser	Leu	Val	Ser	Lys	Ser				
				325					330					335					
Tyr	Ser	Glu	Pro	Val	Asp	Val	Lys	Thr	Ser	Gln	Pro	Pro	Gln	Leu	Ile				
			340					345					350						
Asn	Ser	Lys	Pro	Ser	Val	Phe	His	Gly	Pro	Ser	Gln	Ala	His	Ser	Ala				
		355					360					365							
Leu	Tyr	Leu	Ser	Ser	His	Tyr	His	Gln	Gln	Pro	Gly	Met	Asn	Pro	His				
	370					375					380								
Leu	Thr	Ala	Met	His	Pro	Ser	Leu	Pro	Arg	Asn	Ile	Ala	Pro	Lys	Pro				
385					390					395					400				
Asn	Asn	Gln	Met	Pro	Val	Thr	Val	Ser	Ile	Ala	Asn	Met	Ala	Val	Ser				
				405					410					415					
Pro	Pro	Pro	Pro	Leu	Gln	Ile	Ser	Pro	Pro	Leu	His	Gln	His	Leu	Asn				

420                      425                      430  
 Met Gln Gln His Gln Pro Leu Thr Met Gln Gln Pro Leu Gly Asn Gln  
                     435                      440                      445  
 Leu Pro Met Gln Val Gln Ser Ala Leu His Ser Pro Thr Met Gln Gln  
                     450                      455                      460  
 Gly Phe Thr Leu Gln Pro Asp Tyr Gln Thr Ile Ile Asn Pro Thr Ser  
                     465                      470                      475                      480  
 Thr Ala Ala Gln Val Val Thr Gln Ala Met Glu Tyr Val Arg Ser Gly  
                     485                      490                      495  
 Cys Arg Asn Pro Pro Pro Gln Pro Val Asp Trp Asn Asn Asp Tyr Cys  
                     500                      505                      510  
 Ser Ser Gly Gly Met Gln Arg Asp Lys Ala Leu Tyr Leu Thr  
                     515                      520                      525  
  
 <210> 135  
 <211> 506  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 135  
 Met Leu Ser Lys Val Leu Pro Val Leu Leu Gly Ile Leu Leu Ile Leu  
 1                      5                      10                      15  
 Gln Ser Arg Val Glu Gly Pro Gln Thr Glu Ser Lys Asn Glu Ala Ser  
                     20                      25                      30  
 Ser Arg Asp Val Val Tyr Gly Pro Gln Pro Gln Pro Leu Glu Asn Gln  
                     35                      40                      45  
 Leu Leu Ser Glu Glu Thr Lys Ser Thr Glu Thr Glu Thr Gly Ser Arg  
                     50                      55                      60  
 Val Gly Lys Leu Pro Glu Ala Ser Arg Ile Leu Asn Thr Ile Leu Ser  
 65                      70                      75                      80  
 Asn Tyr Asp His Lys Leu Arg Pro Gly Ile Gly Glu Lys Pro Thr Val  
                     85                      90                      95  
 Val Thr Val Glu Ile Ser Val Asn Ser Leu Gly Pro Leu Ser Ile Leu  
                     100                      105                      110  
 Asp Met Glu Tyr Thr Ile Asp Ile Ile Phe Ser Gln Thr Trp Tyr Asp  
                     115                      120                      125



Glu Arg Leu Cys Tyr Asn Asp Thr Phe Glu Ser Leu Val Leu Asn Gly  
 130 135 140  
 Asn Val Val Ser Gln Leu Trp Ile Pro Asp Thr Phe Phe Arg Asn Ser  
 145 150 155 160  
 Lys Arg Thr His Glu His Glu Ile Thr Met Pro Asn Gln Met Val Arg  
 165 170 175  
 Ile Tyr Lys Asp Gly Lys Val Leu Tyr Thr Ile Arg Met Thr Ile Asp  
 180 185 190  
 Ala Gly Cys Ser Leu His Met Leu Arg Phe Pro Met Asp Ser His Ser  
 195 200 205  
 Cys Pro Leu Ser Phe Ser Ser Phe Ser Tyr Pro Glu Asn Glu Met Ile  
 210 215 220  
 Tyr Lys Trp Glu Asn Phe Lys Leu Glu Ile Asn Glu Lys Asn Ser Trp  
 225 230 235 240  
 Lys Leu Phe Gln Phe Asp Phe Thr Gly Val Ser Asn Lys Thr Glu Ile  
 245 250 255  
 Ile Thr Thr Pro Val Gly Asp Phe Met Val Met Thr Ile Phe Phe Asn  
 260 265 270  
 Val Ser Arg Arg Phe Gly Tyr Val Ala Phe Gln Asn Tyr Val Pro Ser  
 275 280 285  
 Ser Val Thr Thr Met Leu Ser Trp Val Ser Phe Trp Ile Lys Thr Glu  
 290 295 300  
 Ser Ala Pro Ala Arg Thr Ser Leu Gly Ile Thr Ser Val Leu Thr Met  
 305 310 315 320  
 Thr Thr Leu Gly Thr Phe Ser Arg Lys Asn Phe Pro Arg Val Ser Tyr  
 325 330 335  
 Ile Thr Ala Leu Asp Phe Tyr Ile Ala Ile Cys Phe Val Phe Cys Phe  
 340 345 350  
 Cys Ala Leu Leu Glu Phe Ala Val Leu Asn Phe Leu Ile Tyr Asn Gln  
 355 360 365  
 Thr Lys Ala His Ala Ser Pro Lys Leu Arg His Pro Arg Ile Asn Ser  
 370 375 380

Arg Ala His Ala Arg Thr Arg Ala Arg Ser Arg Ala Cys Ala Arg Gln  
385 390 395 400

His Gln Glu Ala Phe Val Cys Gln Ile Val Thr Thr Glu Gly Ser Asp  
405 410 415

Gly Glu Glu Arg Pro Ser Cys Ser Ala Gln Gln Pro Pro Ser Pro Gly  
420 425 430

Ser Pro Glu Gly Pro Arg Ser Leu Cys Ser Lys Leu Ala Cys Cys Glu  
435 440 445

Trp Cys Lys Arg Phe Lys Lys Tyr Phe Cys Met Val Pro Asp Cys Glu  
450 455 460

Gly Ser Thr Trp Gln Gln Gly Arg Leu Cys Ile His Val Tyr Arg Leu  
465 470 475 480

Asp Asn Tyr Ser Arg Val Val Phe Pro Val Thr Phe Phe Phe Phe Asn  
485 490 495

Val Leu Tyr Trp Leu Val Cys Leu Asn Leu  
500 505

<210> 136  
<211> 1581  
<212> PRT  
<213> Homo sapiens

<400> 136

Met Arg Lys Arg Lys Ile Ser Val Cys Gln Gln Thr Trp Ala Leu Leu  
1 5 10 15

Cys Lys Asn Phe Leu Lys Lys Trp Arg Met Lys Arg Glu Ser Leu Met  
20 25 30

Glu Trp Leu Asn Ser Leu Leu Leu Leu Cys Leu Tyr Ile Tyr Pro  
35 40 45

His Ser His Gln Val Asn Asp Phe Ser Ser Leu Leu Thr Met Asp Leu  
50 55 60

Gly Arg Val Asp Thr Phe Asn Glu Ser Arg Phe Ser Val Val Tyr Thr  
65 70 75 80

Pro Val Thr Asn Thr Thr Gln Gln Ile Met Asn Lys Val Ala Ser Thr  
85 90 95

Pro Phe Leu Ala Gly Lys Glu Val Leu Gly Leu Pro Asp Glu Glu Ser  
 100 105 110  
 Ile Lys Glu Phe Thr Ala Asn Tyr Pro Glu Glu Ile Val Arg Val Thr  
 115 120 125  
 Phe Thr Asn Thr Tyr Ser Tyr His Leu Lys Phe Leu Leu Gly His Gly  
 130 135 140  
 Met Pro Ala Lys Lys Glu His Lys Asp His Thr Ala His Cys Tyr Glu  
 145 150 155 160  
 Thr Asn Glu Asp Val Tyr Cys Glu Val Ser Val Phe Trp Lys Glu Gly  
 165 170 175  
 Phe Val Ala Leu Gln Ala Ala Ile Asn Ala Ala Ile Ile Glu Ile Thr  
 180 185 190  
 Thr Asn His Ser Val Met Glu Glu Leu Met Ser Val Thr Gly Lys Asn  
 195 200 205  
 Met Lys Met His Ser Phe Ile Gly Gln Ser Gly Val Ile Thr Asp Leu  
 210 215 220  
 Tyr Leu Phe Ser Cys Ile Ile Ser Phe Ser Ser Phe Ile Tyr Tyr Ala  
 225 230 235 240  
 Ser Val Asn Val Thr Arg Glu Arg Lys Arg Met Lys Ala Leu Met Thr  
 245 250 255  
 Met Met Gly Leu Arg Asp Ser Ala Phe Trp Leu Ser Trp Gly Leu Leu  
 260 265 270  
 Tyr Ala Gly Phe Ile Phe Ile Met Ala Leu Phe Leu Ala Leu Val Ile  
 275 280 285  
 Arg Ser Thr Gln Phe Ile Ile Leu Ser Gly Phe Met Val Val Phe Ser  
 290 295 300  
 Leu Phe Leu Leu Tyr Gly Leu Ser Leu Val Ala Leu Ala Phe Leu Met  
 305 310 315 320  
 Ser Ile Leu Val Lys Lys Ser Phe Leu Thr Gly Leu Val Val Phe Leu  
 325 330 335  
 Leu Thr Val Phe Trp Gly Cys Leu Gly Phe Thr Ser Leu Tyr Arg His  
 340 345 350

Leu Pro Ala Ser Leu Glu Trp Ile Leu Ser Leu Leu Ser Pro Phe Ala  
 355 360 365  
 Phe Met Leu Gly Met Ala Gln Leu Leu His Leu Asp Tyr Asp Leu Asn  
 370 375 380  
 Ser Asn Ala Phe Pro His Pro Ser Asp Gly Ser Asn Leu Ile Val Ala  
 385 390 395 400  
 Thr Asn Phe Met Leu Ala Phe Asp Thr Cys Leu Tyr Leu Ala Leu Ala  
 405 410 415  
 Ile Tyr Phe Glu Lys Ile Leu Pro Asn Glu Tyr Gly His Arg Arg Pro  
 420 425 430  
 Pro Leu Phe Phe Leu Lys Ser Ser Phe Trp Ser Gln Thr Gln Lys Thr  
 435 440 445  
 Asp His Val Ala Leu Glu Asp Glu Met Asp Ala Asp Pro Ser Phe His  
 450 455 460  
 Asp Ser Phe Glu Gln Ala Pro Pro Glu Phe Gln Gly Lys Glu Ala Ile  
 465 470 475 480  
 Arg Ile Arg Asn Val Thr Lys Glu Tyr Lys Gly Lys Pro Asp Lys Ile  
 485 490 495  
 Glu Ala Leu Lys Asp Leu Val Phe Asp Ile Tyr Glu Gly Gln Ile Thr  
 500 505 510  
 Ala Ile Leu Gly His Ser Gly Ala Gly Lys Ser Thr Leu Leu Asn Ile  
 515 520 525  
 Leu Ser Gly Leu Ser Val Pro Thr Lys Gly Ser Val Thr Ile Tyr Asn  
 530 535 540  
 Asn Lys Leu Ser Glu Met Ala Asp Leu Glu Asn Leu Ser Lys Leu Thr  
 545 550 555 560  
 Gly Val Cys Pro Gln Ser Asn Val Gln Phe Asp Phe Leu Thr Val Arg  
 565 570 575  
 Glu Asn Leu Arg Leu Phe Ala Lys Ile Lys Gly Ile Leu Pro Gln Glu  
 580 585 590  
 Val Asp Lys Glu Ile Phe Leu Leu Asp Glu Pro Thr Ala Gly Leu Asp  
 595 600 605

Pro Phe Ser Arg His Gln Val Trp Asn Leu Leu Lys Glu Arg Lys Thr  
 610 615 620  
 Asp Arg Val Ile Leu Phe Ser Thr Gln Phe Met Asp Glu Ala Asp Ile  
 625 630 635 640  
 Leu Ala Asp Arg Lys Val Phe Leu Ser Gln Gly Lys Leu Lys Cys Ala  
 645 650 655  
 Gly Ser Ser Leu Phe Leu Lys Lys Lys Trp Gly Ile Gly Tyr His Leu  
 660 665 670  
 Ser Leu Gln Leu Asn Glu Ile Cys Val Glu Glu Asn Ile Thr Ser Leu  
 675 680 685  
 Val Lys Gln His Ile Pro Asp Ala Lys Leu Ser Ala Lys Ser Glu Gly  
 690 695 700  
 Lys Leu Ile Tyr Thr Leu Pro Leu Glu Arg Thr Asn Lys Phe Pro Glu  
 705 710 715 720  
 Leu Tyr Lys Asp Leu Asp Ser Tyr Pro Asp Leu Gly Ile Glu Asn Tyr  
 725 730 735  
 Gly Val Ser Met Thr Thr Leu Asn Glu Val Phe Leu Lys Leu Glu Gly  
 740 745 750  
 Lys Ser Thr Ile Asn Glu Ser Asp Ile Ala Ile Leu Gly Glu Val Gln  
 755 760 765  
 Ala Glu Lys Ala Asp Asp Thr Glu Arg Leu Val Glu Met Glu Gln Val  
 770 775 780  
 Leu Ser Ser Leu Asn Lys Met Arg Lys Thr Ile Gly Gly Val Ala Leu  
 785 790 795 800  
 Trp Arg Gln Gln Ile Cys Ala Ile Ala Arg Val Arg Leu Leu Lys Leu  
 805 810 815  
 Lys His Glu Arg Lys Ala Leu Leu Ala Leu Leu Leu Ile Leu Met Ala  
 820 825 830  
 Gly Phe Cys Pro Leu Leu Val Glu Tyr Thr Met Val Lys Ile Tyr Gln  
 835 840 845  
 Asn Ser Tyr Thr Trp Glu Leu Ser Pro His Leu Tyr Phe Leu Ala Pro  
 850 855 860

Gly Gln Gln Pro His Asp Pro Leu Thr Gln Leu Leu Ile Ile Asn Lys  
865 870 875 880

Thr Gly Ala Ser Ile Asp Asp Phe Ile Gln Ser Val Glu His Gln Asn  
885 890 895

Ile Ala Leu Glu Val Asp Ala Phe Gly Thr Arg Asn Gly Thr Asp Asp  
900 905 910

Pro Ser Tyr Asn Gly Ala Ile Thr Val Cys Cys Asn Glu Lys Asn Tyr  
915 920 925

Ser Phe Ser Leu Ala Cys Asn Ala Lys Arg Leu Asn Cys Phe Pro Val  
930 935 940

Leu Met Asp Ile Val Ser Asn Gly Leu Leu Gly Met Val Lys Pro Ser  
945 950 955 960

Val His Ile Arg Thr Glu Arg Ser Thr Phe Leu Glu Asn Gly Gln Asp  
965 970 975

Asn Pro Ile Gly Phe Leu Ala Tyr Ile Met Phe Trp Leu Val Leu Thr  
980 985 990

Ser Ser Cys Pro Pro Tyr Ile Ala Met Ser Ser Ile Asp Asp Tyr Lys  
995 1000 1005

Asn Arg Ala Arg Ser Gln Leu Arg Ile Ser Gly Leu Ser Pro Ser  
1010 1015 1020

Ala Tyr Trp Phe Gly Gln Ala Leu Val Asp Val Ser Leu Tyr Phe  
1025 1030 1035

Leu Val Phe Val Phe Ile Tyr Leu Met Ser Tyr Ile Ser Asn Phe  
1040 1045 1050

Glu Asp Met Leu Leu Thr Ile Ile His Ile Ile Gln Ile Pro Cys  
1055 1060 1065

Ala Val Gly Tyr Ser Phe Ser Leu Ile Phe Met Thr Tyr Val Ile  
1070 1075 1080

Ser Phe Ile Phe Arg Lys Gly Arg Lys Asn Ser Gly Ile Trp Ser  
1085 1090 1095

Phe Cys Phe Tyr Val Val Thr Val Phe Ser Val Ala Gly Phe Ala  
1100 1105 1110

Phe Ser Ile Phe Glu Ser Asp Ile Pro Phe Ile Phe Thr Phe Leu  
 1115 1120 1125  
 Ile Pro Pro Ala Thr Met Ile Gly Cys Leu Phe Leu Ser Ser His  
 1130 1135 1140  
 Leu Leu Phe Ser Ser Leu Phe Ser Glu Glu Arg Met Asp Val Gln  
 1145 1150 1155  
 Pro Phe Leu Val Phe Leu Ile Pro Phe Leu His Phe Ile Ile Phe  
 1160 1165 1170  
 Leu Phe Thr Leu Arg Cys Leu Glu Trp Lys Phe Gly Lys Lys Ser  
 1175 1180 1185  
 Met Arg Lys Asp Pro Phe Phe Arg Ile Ser Pro Arg Ser Ser Asp  
 1190 1195 1200  
 Val Cys Gln Asn Pro Glu Glu Pro Glu Gly Glu Asp Glu Asp Val  
 1205 1210 1215  
 Gln Met Glu Arg Val Arg Thr Ala Asn Ala Leu Asn Ser Thr Asn  
 1220 1225 1230  
 Phe Asp Glu Lys Pro Val Ile Ile Ala Ser Cys Leu Arg Lys Glu  
 1235 1240 1245  
 Tyr Ala Gly Lys Arg Lys Gly Cys Phe Ser Lys Arg Lys Asn Lys  
 1250 1255 1260  
 Ile Ala Thr Arg Asn Val Ser Phe Cys Val Arg Lys Gly Glu Val  
 1265 1270 1275  
 Leu Gly Leu Leu Gly His Asn Gly Ala Gly Lys Ser Thr Ser Ile  
 1280 1285 1290  
 Lys Val Ile Thr Gly Asp Thr Lys Pro Thr Ala Gly Gln Val Leu  
 1295 1300 1305  
 Leu Lys Gly Ser Gly Gly Gly Asp Ala Leu Glu Phe Leu Gly Tyr  
 1310 1315 1320  
 Cys Pro Gln Glu Asn Ala Leu Trp Pro Asn Leu Thr Val Arg Gln  
 1325 1330 1335  
 His Leu Glu Val Tyr Ala Ala Val Lys Gly Leu Arg Lys Gly Asp  
 1340 1345 1350

Ala Glu Val Ala Ile Thr Arg Leu Val Asp Ala Leu Lys Leu Gln  
 1355 1360 1365  
 Asp Gln Leu Lys Ser Pro Val Lys Thr Leu Ser Glu Gly Ile Lys  
 1370 1375 1380  
 Arg Lys Leu Cys Phe Val Leu Ser Ile Leu Gly Asn Pro Ser Val  
 1385 1390 1395  
 Val Leu Leu Asp Glu Pro Ser Thr Gly Met Asp Pro Glu Gly Gln  
 1400 1405 1410  
 Gln Gln Met Trp Gln Ala Ile Arg Ala Thr Phe Arg Asn Thr Glu  
 1415 1420 1425  
 Arg Gly Ala Leu Leu Thr Thr His Tyr Met Ala Glu Ala Glu Ala  
 1430 1435 1440  
 Val Cys Asp Arg Val Ala Ile Met Val Ser Gly Arg Leu Arg Cys  
 1445 1450 1455  
 Ile Gly Ser Ile Gln His Leu Lys Ser Lys Phe Gly Lys Asp Tyr  
 1460 1465 1470  
 Leu Leu Glu Met Lys Val Lys Asn Leu Ala Gln Val Glu Pro Leu  
 1475 1480 1485  
 His Ala Glu Ile Leu Arg Leu Phe Pro Gln Ala Ala Arg Gln Glu  
 1490 1495 1500  
 Arg Tyr Ser Ser Leu Met Val Tyr Lys Leu Pro Val Glu Asp Val  
 1505 1510 1515  
 Gln Pro Leu Ala Gln Ala Phe Phe Lys Leu Glu Lys Val Lys Gln  
 1520 1525 1530  
 Ser Phe Asp Leu Glu Glu Tyr Ser Leu Ser Gln Ser Thr Leu Glu  
 1535 1540 1545  
 Gln Val Phe Leu Glu Leu Ser Lys Glu Gln Glu Leu Gly Asp Phe  
 1550 1555 1560  
 Glu Glu Asp Phe Asp Pro Ser Val Lys Trp Lys Leu Leu Pro Gln  
 1565 1570 1575  
 Glu Glu Pro  
 1580



<210> 137  
 <211> 422  
 <212> PRT  
 <213> Homo sapiens

<400> 137

Met Ser Ser Ser Cys Ser Gly Leu Ser Arg Val Leu Val Ala Val Ala  
 1 5 10 15  
 Thr Ala Leu Val Ser Ala Ser Ser Pro Cys Pro Gln Ala Trp Gly Pro  
 20 25 30  
 Pro Gly Val Gln Tyr Gly Gln Pro Gly Arg Ser Val Lys Leu Cys Cys  
 35 40 45  
 Pro Gly Val Thr Ala Gly Asp Pro Val Ser Trp Phe Arg Asp Gly Glu  
 50 55 60  
 Pro Lys Leu Leu Gln Gly Pro Asp Ser Gly Leu Gly His Glu Leu Val  
 65 70 75 80  
 Leu Ala Gln Ala Asp Ser Thr Asp Glu Gly Thr Tyr Ile Cys Gln Thr  
 85 90 95  
 Leu Asp Gly Ala Leu Gly Gly Thr Val Thr Leu Gln Leu Gly Tyr Pro  
 100 105 110  
 Pro Ala Arg Pro Val Val Ser Cys Gln Ala Ala Asp Tyr Glu Asn Phe  
 115 120 125  
 Ser Cys Thr Trp Ser Pro Ser Gln Ile Ser Gly Leu Pro Thr Arg Tyr  
 130 135 140  
 Leu Thr Ser Tyr Arg Lys Lys Thr Val Leu Gly Ala Asp Ser Gln Arg  
 145 150 155 160  
 Arg Ser Pro Ser Thr Gly Pro Trp Pro Cys Pro Gln Asp Pro Leu Gly  
 165 170 175  
 Ala Ala Arg Cys Val Val His Gly Ala Glu Phe Trp Ser Gln Tyr Arg  
 180 185 190  
 Ile Asn Val Thr Glu Val Asn Pro Leu Gly Ala Ser Thr Arg Leu Leu  
 195 200 205  
 Asp Val Ser Leu Gln Ser Ile Leu Arg Pro Asp Pro Pro Gln Gly Leu  
 210 215 220

Arg Val Glu Ser Val Pro Gly Tyr Pro Arg Arg Leu Arg Ala Ser Trp  
 225 230 235 240

Thr Tyr Pro Ala Ser Trp Pro Cys Gln Pro His Phe Leu Leu Lys Phe  
 245 250 255

Arg Leu Gln Tyr Arg Pro Ala Gln His Pro Ala Trp Ser Thr Val Glu  
 260 265 270

Pro Ala Gly Leu Glu Glu Val Ile Thr Asp Ala Val Ala Gly Leu Pro  
 275 280 285

His Ala Val Arg Val Ser Ala Arg Asp Phe Leu Asp Ala Gly Thr Trp  
 290 295 300

Ser Thr Trp Ser Pro Glu Ala Trp Gly Thr Pro Ser Thr Gly Thr Ile  
 305 310 315 320

Pro Lys Glu Ile Pro Ala Trp Gly Gln Leu His Thr Gln Pro Glu Val  
 325 330 335

Glu Pro Gln Val Asp Ser Pro Ala Pro Pro Arg Pro Ser Leu Gln Pro  
 340 345 350

His Pro Arg Leu Leu Asp His Arg Asp Ser Val Glu Gln Val Ala Val  
 355 360 365

Leu Ala Ser Leu Gly Ile Leu Ser Phe Leu Gly Leu Val Ala Gly Ala  
 370 375 380

Leu Ala Leu Gly Leu Trp Leu Arg Leu Arg Arg Gly Gly Lys Asp Gly  
 385 390 395 400

Ser Pro Lys Pro Gly Phe Leu Ala Ser Val Ile Pro Val Asp Arg Arg  
 405 410 415

Pro Gly Ala Pro Asn Leu  
 420

<210> 138  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 138

Ile Glu Pro Leu Ile Ser Ala Phe His Lys Val Glu Lys Phe Ala Lys  
 1 5 10 15

Glu Leu Gln Gly Lys Thr Asp Asn Gln Asn Asp Pro Glu Gly Asp Gln

20

25

30

Glu Asn

<210> 139  
 <211> 1181  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 139

Met Gly Pro Glu Arg Thr Gly Ala Ala Pro Leu Pro Leu Leu Val  
 1 5 10 15

Leu Ala Leu Ser Gln Gly Ile Leu Asn Cys Cys Leu Ala Tyr Asn Val  
 20 25 30

Gly Leu Pro Glu Ala Lys Ile Phe Ser Gly Pro Ser Ser Glu Gln Phe  
 35 40 45

Gly Tyr Ala Val Gln Gln Phe Ile Asn Pro Lys Gly Asn Trp Leu Leu  
 50 55 60

Val Gly Ser Pro Trp Ser Gly Phe Pro Glu Asn Arg Met Gly Asp Val  
 65 70 75 80

Tyr Lys Cys Pro Val Asp Leu Ser Thr Ala Thr Cys Glu Lys Leu Asn  
 85 90 95

Leu Gln Thr Ser Thr Ser Ile Pro Asn Val Thr Glu Met Lys Thr Asn  
 100 105 110

Met Ser Leu Gly Leu Ile Leu Thr Arg Asn Met Gly Thr Gly Gly Phe  
 115 120 125

Leu Thr Cys Gly Pro Leu Trp Ala Gln Gln Cys Gly Asn Gln Tyr Tyr  
 130 135 140

Thr Thr Gly Val Cys Ser Asp Ile Ser Pro Asp Phe Gln Leu Ser Ala  
 145 150 155 160

Ser Phe Ser Pro Ala Thr Gln Pro Cys Pro Ser Leu Ile Asp Val Val  
 165 170 175

Val Val Cys Asp Glu Ser Asn Ser Ile Tyr Pro Trp Asp Ala Val Lys  
 180 185 190

Asn Phe Leu Glu Lys Phe Val Gln Gly Leu Asp Ile Gly Pro Thr Lys  
 195 200 205

Thr Gln Val Gly Leu Ile Gln Tyr Ala Asn Asn Pro Arg Val Val Phe  
 210 215 220  
 Asn Leu Asn Thr Tyr Lys Thr Lys Glu Glu Met Ile Val Ala Thr Ser  
 225 230 235 240  
 Gln Thr Ser Gln Tyr Gly Gly Asp Leu Thr Asn Thr Phe Gly Ala Ile  
 245 250 255  
 Gln Tyr Ala Arg Lys Tyr Ala Tyr Ser Ala Ala Ser Gly Gly Arg Arg  
 260 265 270  
 Ser Ala Thr Lys Val Met Val Val Val Thr Asp Gly Glu Ser His Asp  
 275 280 285  
 Gly Ser Met Leu Lys Ala Val Ile Asp Gln Cys Asn His Asp Asn Ile  
 290 295 300  
 Leu Arg Phe Gly Ile Ala Val Leu Gly Tyr Leu Asn Arg Asn Ala Leu  
 305 310 315 320  
 Asp Thr Lys Asn Leu Ile Lys Glu Ile Lys Ala Ile Ala Ser Ile Pro  
 325 330 335  
 Thr Glu Arg Tyr Phe Phe Asn Val Ser Asp Glu Ala Ala Leu Leu Glu  
 340 345 350  
 Lys Ala Gly Thr Leu Gly Glu Gln Ile Phe Ser Ile Glu Gly Thr Val  
 355 360 365  
 Gln Gly Gly Asp Asn Phe Gln Met Glu Met Ser Gln Val Gly Phe Ser  
 370 375 380  
 Ala Asp Tyr Ser Ser Gln Asn Asp Ile Leu Met Leu Gly Ala Val Gly  
 385 390 395 400  
 Ala Phe Gly Trp Ser Gly Thr Ile Val Gln Lys Thr Ser His Gly His  
 405 410 415  
 Leu Ile Phe Pro Lys Gln Ala Phe Asp Gln Ile Leu Gln Asp Arg Asn  
 420 425 430  
 His Ser Ser Tyr Leu Gly Tyr Ser Val Ala Ala Ile Ser Thr Gly Glu  
 435 440 445  
 Ser Thr His Phe Val Ala Gly Ala Pro Arg Ala Asn Tyr Thr Gly Gln  
 450 455 460

Ile Val Leu Tyr Ser Val Asn Glu Asn Gly Asn Ile Thr Val Ile Gln  
 465 470 475 480  
 Ala His Arg Gly Asp Gln Ile Gly Ser Tyr Phe Gly Ser Val Leu Cys  
 485 490 495  
 Ser Val Asp Val Asp Lys Asp Thr Ile Thr Asp Val Leu Leu Val Gly  
 500 505 510  
 Ala Pro Met Tyr Met Ser Asp Leu Lys Lys Glu Glu Gly Arg Val Tyr  
 515 520 525  
 Leu Phe Thr Ile Lys Lys Gly Ile Leu Gly Gln His Gln Phe Leu Glu  
 530 535 540  
 Gly Pro Glu Gly Ile Glu Asn Thr Arg Phe Gly Ser Ala Ile Ala Ala  
 545 550 555 560  
 Leu Ser Asp Ile Asn Met Asp Gly Phe Asn Asp Val Ile Val Gly Ser  
 565 570 575  
 Pro Leu Glu Asn Gln Asn Ser Gly Ala Val Tyr Ile Tyr Asn Gly His  
 580 585 590  
 Gln Gly Thr Ile Arg Thr Lys Tyr Ser Gln Lys Ile Leu Gly Ser Asp  
 595 600 605  
 Gly Ala Phe Arg Ser His Leu Gln Tyr Phe Gly Arg Ser Leu Asp Gly  
 610 615 620  
 Tyr Gly Asp Leu Asn Gly Asp Ser Ile Thr Asp Val Ser Ile Gly Ala  
 625 630 635 640  
 Phe Gly Gln Val Val Gln Leu Trp Ser Gln Ser Ile Ala Asp Val Ala  
 645 650 655  
 Ile Glu Ala Ser Phe Thr Pro Glu Lys Ile Thr Leu Val Asn Lys Asn  
 660 665 670  
 Ala Gln Ile Ile Leu Lys Leu Cys Phe Ser Ala Lys Phe Arg Pro Thr  
 675 680 685  
 Lys Gln Asn Asn Gln Val Ala Ile Val Tyr Asn Ile Thr Leu Asp Ala  
 690 695 700  
 Asp Gly Phe Ser Ser Arg Val Thr Ser Arg Gly Leu Phe Lys Glu Asn  
 705 710 715 720

Asn Glu Arg Cys Leu Gln Lys Asn Met Val Val Asn Gln Ala Gln Ser  
 725 730 735  
 Cys Pro Glu His Ile Ile Tyr Ile Gln Glu Pro Ser Asp Val Val Asn  
 740 745 750  
 Ser Leu Asp Leu Arg Val Asp Ile Ser Leu Glu Asn Pro Gly Thr Ser  
 755 760 765  
 Pro Ala Leu Glu Ala Tyr Ser Glu Thr Ala Lys Val Phe Ser Ile Pro  
 770 775 780  
 Phe His Lys Asp Cys Gly Glu Asp Gly Leu Cys Ile Ser Asp Leu Val  
 785 790 795 800  
 Leu Asp Val Arg Gln Ile Pro Ala Ala Gln Glu Gln Pro Phe Ile Val  
 805 810 815  
 Ser Asn Gln Asn Lys Arg Leu Thr Phe Ser Val Thr Leu Lys Asn Lys  
 820 825 830  
 Arg Glu Ser Ala Tyr Asn Thr Gly Ile Val Val Asp Phe Ser Glu Asn  
 835 840 845  
 Leu Phe Phe Ala Ser Phe Ser Leu Pro Val Asp Gly Thr Glu Val Thr  
 850 855 860  
 Cys Gln Val Ala Ala Ser Gln Lys Ser Val Ala Cys Asp Val Gly Tyr  
 865 870 875 880  
 Pro Ala Leu Lys Arg Glu Gln Gln Val Thr Phe Thr Ile Asn Phe Asp  
 885 890 895  
 Phe Asn Leu Gln Asn Leu Gln Asn Gln Ala Ser Leu Ser Phe Gln Ala  
 900 905 910  
 Leu Ser Glu Ser Gln Glu Glu Asn Lys Ala Asp Asn Leu Val Asn Leu  
 915 920 925  
 Lys Ile Pro Leu Leu Tyr Asp Ala Glu Ile His Leu Thr Arg Ser Thr  
 930 935 940  
 Asn Ile Asn Phe Tyr Glu Ile Ser Ser Asp Gly Asn Val Pro Ser Ile  
 945 950 955 960  
 Val His Ser Phe Glu Asp Val Gly Pro Lys Phe Ile Phe Ser Leu Lys  
 965 970 975

Val Thr Thr Gly Ser Val Pro Val Ser Met Ala Thr Val Ile Ile His  
 980 985 990

Ile Pro Gln Tyr Thr Lys Glu Lys Asn Pro Leu Met Tyr Leu Thr Gly  
 995 1000 1005

Val Gln Thr Asp Lys Ala Gly Asp Ile Ser Cys Asn Ala Asp Ile  
 1010 1015 1020

Asn Pro Leu Lys Ile Gly Gln Thr Ser Ser Ser Val Ser Phe Lys  
 1025 1030 1035

Ser Glu Asn Phe Arg His Thr Lys Glu Leu Asn Cys Arg Thr Ala  
 1040 1045 1050

Ser Cys Ser Asn Val Thr Cys Trp Leu Lys Asp Val His Met Lys  
 1055 1060 1065

Gly Glu Tyr Phe Val Asn Val Thr Thr Arg Ile Trp Asn Gly Thr  
 1070 1075 1080

Phe Ala Ser Ser Thr Phe Gln Thr Val Gln Leu Thr Ala Ala Ala  
 1085 1090 1095

Glu Ile Asn Thr Tyr Asn Pro Glu Ile Tyr Val Ile Glu Asp Asn  
 1100 1105 1110

Thr Val Thr Ile Pro Leu Met Ile Met Lys Pro Asp Glu Lys Ala  
 1115 1120 1125

Glu Val Pro Thr Gly Val Ile Ile Gly Ser Ile Ile Ala Gly Ile  
 1130 1135 1140

Leu Leu Leu Leu Ala Leu Val Ala Ile Leu Trp Lys Leu Gly Phe  
 1145 1150 1155

Phe Lys Arg Lys Tyr Glu Lys Met Thr Lys Asn Pro Asp Glu Ile  
 1160 1165 1170

Asp Glu Thr Thr Glu Leu Ser Ser  
 1175 1180

<210> 140  
 <211> 245  
 <212> PRT  
 <213> Homo sapiens

<400> 140

Met Ala Ala Ala Ile Ala Ser Ser Leu Ile Arg Gln Lys Arg Gln Ala  
 1 5 10 15  
 Arg Glu Arg Glu Lys Ser Asn Ala Cys Lys Cys Val Ser Ser Pro Ser  
 20 25 30  
 Lys Gly Lys Thr Ser Cys Asp Lys Asn Lys Leu Asn Val Phe Ser Arg  
 35 40 45  
 Val Lys Leu Phe Gly Ser Lys Lys Arg Arg Arg Arg Arg Pro Glu Pro  
 50 55 60  
 Gln Leu Lys Gly Ile Val Thr Lys Leu Tyr Ser Arg Gln Gly Tyr His  
 65 70 75 80  
 Leu Gln Leu Gln Ala Asp Gly Thr Ile Asp Gly Thr Lys Asp Glu Asp  
 85 90 95  
 Ser Thr Tyr Thr Leu Phe Asn Leu Ile Pro Val Gly Leu Arg Val Val  
 100 105 110  
 Ala Ile Gln Gly Val Gln Thr Lys Leu Tyr Leu Ala Met Asn Ser Glu  
 115 120 125  
 Gly Tyr Leu Tyr Thr Ser Glu Leu Phe Thr Pro Glu Cys Lys Phe Lys  
 130 135 140  
 Glu Ser Val Phe Glu Asn Tyr Tyr Val Thr Tyr Ser Ser Met Ile Tyr  
 145 150 155 160  
 Arg Gln Gln Gln Ser Gly Arg Gly Trp Tyr Leu Gly Leu Asn Lys Glu  
 165 170 175  
 Gly Glu Ile Met Lys Gly Asn His Val Lys Lys Asn Lys Pro Ala Ala  
 180 185 190  
 His Phe Leu Pro Lys Pro Leu Lys Val Ala Met Tyr Lys Glu Pro Ser  
 195 200 205  
 Leu His Asp Leu Thr Glu Phe Ser Arg Ser Gly Ser Gly Thr Pro Thr  
 210 215 220  
 Lys Ser Arg Ser Val Ser Gly Val Leu Asn Gly Gly Lys Ser Met Ser  
 225 230 235 240  
 His Asn Glu Ser Thr  
 245



<210> 141  
 <211> 202  
 <212> PRT  
 <213> Homo sapiens

<400> 141

Met Glu Leu Trp Gly Ala Tyr Leu Leu Leu Cys Leu Phe Ser Leu Leu  
 1 5 10 15

Thr Gln Val Thr Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val  
 20 25 30

Asn Ala Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys  
 35 40 45

Ser Arg Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln  
 50 55 60

Gln Ala Leu Gln Thr Val Cys Leu Lys Gly Thr Lys Val His Met Lys  
 65 70 75 80

Cys Phe Leu Ala Phe Thr Gln Thr Lys Thr Phe His Glu Ala Ser Glu  
 85 90 95

Asp Cys Ile Ser Arg Gly Gly Thr Leu Ser Thr Pro Gln Thr Gly Ser  
 100 105 110

Glu Asn Asp Ala Leu Tyr Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu  
 115 120 125

Ala Glu Ile Trp Leu Gly Leu Asn Asp Met Ala Ala Glu Gly Thr Trp  
 130 135 140

Val Asp Met Thr Gly Ala Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu  
 145 150 155 160

Ile Thr Ala Gln Pro Asp Gly Gly Lys Thr Glu Asn Cys Ala Val Leu  
 165 170 175

Ser Gly Ala Ala Asn Gly Lys Trp Phe Asp Lys Arg Cys Arg Asp Gln  
 180 185 190

Leu Pro Tyr Ile Cys Gln Phe Gly Ile Val  
 195 200

<210> 142  
 <211> 638  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 142

Met Asp Leu Trp Gln Leu Leu Leu Thr Leu Ala Leu Ala Gly Ser Ser  
 1 5 10 15

Asp Ala Phe Ser Gly Ser Glu Ala Thr Ala Ala Ile Leu Ser Arg Ala  
 20 25 30

Pro Trp Ser Leu Gln Ser Val Asn Pro Gly Leu Lys Thr Asn Ser Ser  
 35 40 45

Lys Glu Pro Lys Phe Thr Lys Cys Arg Ser Pro Glu Arg Glu Thr Phe  
 50 55 60

Ser Cys His Trp Thr Asp Glu Val His His Gly Thr Lys Asn Leu Gly  
 65 70 75 80

Pro Ile Gln Leu Phe Tyr Thr Arg Arg Asn Thr Gln Glu Trp Thr Gln  
 85 90 95

Glu Trp Lys Glu Cys Pro Asp Tyr Val Ser Ala Gly Glu Asn Ser Cys  
 100 105 110

Tyr Phe Asn Ser Ser Phe Thr Ser Ile Trp Ile Pro Tyr Cys Ile Lys  
 115 120 125

Leu Thr Ser Asn Gly Gly Thr Val Asp Glu Lys Cys Phe Ser Val Asp  
 130 135 140

Glu Ile Val Gln Pro Asp Pro Pro Ile Ala Leu Asn Trp Thr Leu Leu  
 145 150 155 160

Asn Val Ser Leu Thr Gly Ile His Ala Asp Ile Gln Val Arg Trp Glu  
 165 170 175

Ala Pro Arg Asn Ala Asp Ile Gln Lys Gly Trp Met Val Leu Glu Tyr  
 180 185 190

Glu Leu Gln Tyr Lys Glu Val Asn Glu Thr Lys Trp Lys Met Met Asp  
 195 200 205

Pro Ile Leu Thr Thr Ser Val Pro Val Tyr Ser Leu Lys Val Asp Lys  
 210 215 220

Glu Tyr Glu Val Arg Val Arg Ser Lys Gln Arg Asn Ser Gly Asn Tyr  
 225 230 235 240

Gly Glu Phe Ser Glu Val Leu Tyr Val Thr Leu Pro Gln Met Ser Gln

245 250 255  
 Phe Thr Cys Glu Glu Asp Phe Tyr Phe Pro Trp Leu Leu Ile Ile Ile  
 260 265 270  
 Phe Gly Ile Phe Gly Leu Thr Val Met Leu Phe Val Phe Leu Phe Ser  
 275 280 285  
 Lys Gln Gln Arg Ile Lys Met Leu Ile Leu Pro Pro Val Pro Val Pro  
 290 295 300  
 Lys Ile Lys Gly Ile Asp Pro Asp Leu Leu Lys Glu Gly Lys Leu Glu  
 305 310 315 320  
 Glu Val Asn Thr Ile Leu Ala Ile His Asp Ser Tyr Lys Pro Glu Phe  
 325 330 335  
 His Ser Asp Asp Ser Trp Val Glu Phe Ile Glu Leu Asp Ile Asp Glu  
 340 345 350  
 Pro Asp Glu Lys Thr Glu Glu Ser Asp Thr Asp Arg Leu Leu Ser Ser  
 355 360 365  
 Asp His Glu Lys Ser His Ser Asn Leu Gly Val Lys Asp Gly Asp Ser  
 370 375 380  
 Gly Arg Thr Ser Cys Cys Glu Pro Asp Ile Leu Glu Thr Asp Phe Asn  
 385 390 395 400  
 Ala Asn Asp Ile His Glu Gly Thr Ser Glu Val Ala Gln Pro Gln Arg  
 405 410 415  
 Leu Lys Gly Glu Ala Asp Leu Leu Cys Leu Asp Gln Lys Asn Gln Asn  
 420 425 430  
 Asn Ser Pro Tyr His Asp Ala Cys Pro Ala Thr Gln Gln Pro Ser Val  
 435 440 445  
 Ile Gln Ala Glu Lys Asn Lys Pro Gln Pro Leu Pro Thr Glu Gly Ala  
 450 455 460  
 Glu Ser Thr His Gln Ala Ala His Ile Gln Leu Ser Asn Pro Ser Ser  
 465 470 475 480  
 Leu Ser Asn Ile Asp Phe Tyr Ala Gln Val Ser Asp Ile Thr Pro Ala  
 485 490 495  
 Gly Ser Val Val Leu Ser Pro Gly Gln Lys Ala Gly Met Ser

500                      505                      510  
 Gln Cys Asp Met His Pro Glu Met Val Ser Leu Cys Gln Glu Asn Phe  
     515                      520                      525  
 Leu Met Asp Asn Ala Tyr Phe Cys Glu Ala Asp Ala Lys Lys Cys Ile  
     530                      535                      540  
 Pro Val Ala Pro His Ile Lys Val Glu Ser His Ile Gln Pro Ser Leu  
     545                      550                      555                      560  
 Asn Gln Glu Asp Ile Tyr Ile Thr Thr Glu Ser Leu Thr Thr Ala Ala  
                     565                      570                      575  
 Gly Arg Pro Gly Thr Gly Glu His Val Pro Gly Ser Glu Met Pro Val  
                     580                      585                      590  
 Pro Asp Tyr Thr Ser Ile His Ile Val Gln Ser Pro Gln Gly Leu Ile  
                     595                      600                      605  
 Leu Asn Ala Thr Ala Leu Pro Leu Pro Asp Lys Glu Phe Leu Ser Ser  
     610                      615                      620  
 Cys Gly Tyr Val Ser Thr Asp Gln Leu Asn Lys Ile Met Pro  
     625                      630                      635  
  
 <210> 143  
 <211> 465  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 143  
 Met Ala Ser Gln Leu Thr Gln Arg Gly Ala Leu Phe Leu Leu Phe Phe  
     1                      5                      10                      15  
 Leu Thr Pro Ala Val Thr Pro Thr Trp Tyr Ala Gly Ser Gly Tyr Tyr  
                     20                      25                      30  
 Pro Asp Glu Ser Tyr Asn Glu Val Tyr Ala Glu Glu Val Pro Gln Ala  
                     35                      40                      45  
 Pro Ala Leu Asp Tyr Arg Val Pro Arg Trp Cys Tyr Thr Leu Asn Ile  
     50                      55                      60  
 Gln Asp Gly Glu Ala Thr Cys Tyr Ser Pro Lys Gly Gly Asn Tyr His  
     65                      70                      75                      80  
 Ser Ser Leu Gly Thr Arg Cys Glu Leu Ser Cys Asp Arg Gly Phe Arg  
                     85                      90                      95

Leu Ile Gly Arg Arg Ser Val Gln Cys Leu Pro Ser Arg Arg Trp Ser  
 100 105 110  
 Gly Thr Ala Tyr Cys Arg Gln Met Arg Cys His Ala Leu Pro Phe Ile  
 115 120 125  
 Thr Ser Gly Thr Tyr Thr Cys Thr Asn Gly Val Leu Leu Asp Ser Arg  
 130 135 140  
 Cys Asp Tyr Ser Cys Ser Ser Gly Tyr His Leu Glu Gly Asp Arg Ser  
 145 150 155 160  
 Arg Ile Cys Met Glu Asp Gly Arg Trp Ser Gly Gly Glu Pro Val Cys  
 165 170 175  
 Val Asp Ile Asp Pro Pro Lys Ile Arg Cys Pro His Ser Arg Glu Lys  
 180 185 190  
 Met Ala Glu Pro Glu Lys Leu Thr Ala Arg Val Tyr Trp Asp Pro Pro  
 195 200 205  
 Leu Val Lys Asp Ser Ala Asp Gly Thr Ile Thr Arg Val Thr Leu Arg  
 210 215 220  
 Gly Pro Glu Pro Gly Ser His Phe Pro Glu Gly Glu His Val Ile Arg  
 225 230 235 240  
 Tyr Thr Ala Tyr Asp Arg Ala Tyr Asn Arg Ala Ser Cys Lys Phe Ile  
 245 250 255  
 Val Lys Val Gln Val Arg Arg Cys Pro Thr Leu Lys Pro Pro Gln His  
 260 265 270  
 Gly Tyr Leu Thr Cys Thr Ser Ala Gly Asp Asn Tyr Gly Ala Ser Cys  
 275 280 285  
 Glu Tyr His Cys Asp Gly Gly Tyr Asp Arg Gln Gly Thr Pro Ser Arg  
 290 295 300  
 Val Cys Gln Ser Ser Arg Gln Trp Ser Gly Ser Pro Pro Ile Cys Ala  
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Cys Gly Leu Asp Leu Arg His Val Thr Ile Ile Glu Leu Val Gly Gln  
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Pro Pro Gln Glu Val Gly Arg Ile Arg Glu Gln Gln Leu Ser Ala Asn  
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<400> 144

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Gln Arg Lys Phe Cys Leu Ala Ala Glu Gly Leu Gly Asn Arg Leu Cys  
35 40 45

Phe Leu Glu Pro Thr Ser Glu Ala Lys Tyr Ile Pro Pro Asp Leu Cys  
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Val Cys Asn Phe Val Leu Glu Gln Ser Leu Ser Val Arg Ala Leu Gln  
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Glu Met Leu Ala Asn Thr Gly Glu Asn Gly Gly Glu Gly Ala Ala Gln  
85 90 95

Gly Gly Gly His Arg Thr Leu Leu Tyr Gly His Ala Val Leu Leu Arg  
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 His Ser Phe Ser Gly Met Tyr Leu Thr Cys Leu Thr Thr Ser Arg Ser  
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 Gln Thr Asp Lys Leu Ala Phe Asp Val Gly Leu Arg Glu His Ala Thr  
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 Arg Asn His Lys Val Leu Asp Ile Leu Cys Ser Leu Cys Leu Cys Asn  
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 2525 2530 2535  
 Glu Lys Leu Phe Trp Gly Ile Phe Asp Ser Leu Ser His Lys Lys  
 2540 2545 2550



Tyr Asp Pro Asp Leu Phe Arg Met Ala Leu Pro Cys Leu Ser Ala  
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 Gln Ser Gly Glu Asp Glu Glu Glu Asp Glu Asp Lys Glu Lys Thr  
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 Phe Glu Glu Lys Glu Met Glu Lys Gln Lys Thr Leu Tyr Gln Gln  
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 Asn Ser Leu Thr Glu Tyr Ile Gln Gly Pro Cys Ile Gly Asn Gln  
 3815 3820 3825  
 Gln Ser Leu Ala His Ser Arg Leu Trp Asp Ala Val Val Gly Phe  
 3830 3835 3840  
 Leu His Val Phe Ala Asn Met Gln Met Lys Leu Ser Gln Asp Ser  
 3845 3850 3855  
 Ser Gln Ile Glu Leu Leu Lys Glu Leu Leu Asp Leu Leu Gln Asp  
 3860 3865 3870  
 Met Val Val Met Leu Leu Ser Leu Leu Glu Gly Asn Val Val Asn  
 3875 3880 3885  
 Gly Thr Ile Gly Lys Gln Met Val Asp Thr Leu Val Glu Ser Ser  
 3890 3895 3900  
 Thr Asn Val Glu Met Ile Leu Lys Phe Phe Asp Met Phe Leu Lys  
 3905 3910 3915  
 Leu Lys Asp Leu Thr Ser Ser Asp Thr Phe Lys Glu Tyr Asp Pro  
 3920 3925 3930  
 Asp Gly Lys Gly Ile Ile Ser Lys Lys Glu Phe Gln Lys Ala Met  
 3935 3940 3945  
 Glu Gly Gln Lys Gln Tyr Thr Gln Ser Glu Ile Asp Phe Leu Leu  
 3950 3955 3960  
 Ser Cys Ala Glu Ala Asp Glu Asn Asp Met Phe Asn Tyr Val Asp  
 3965 3970 3975  
 Phe Val Asp Arg Phe His Glu Pro Ala Lys Asp Ile Gly Phe Asn  
 3980 3985 3990

Val Ala Val Leu Leu Thr Asn Leu Ser Glu His Met Pro Asn Asp  
 3995 4000 4005  
 Ser Arg Leu Lys Cys Leu Leu Asp Pro Ala Glu Ser Val Leu Asn  
 4010 4015 4020  
 Tyr Phe Glu Pro Tyr Leu Gly Arg Ile Glu Ile Met Gly Gly Ala  
 4025 4030 4035  
 Lys Lys Ile Glu Arg Val Tyr Phe Glu Ile Ser Glu Ser Ser Arg  
 4040 4045 4050  
 Thr Gln Trp Glu Lys Pro Gln Val Lys Glu Ser Lys Arg Gln Phe  
 4055 4060 4065  
 Ile Phe Asp Val Val Asn Glu Gly Gly Glu Gln Glu Lys Met Glu  
 4070 4075 4080  
 Leu Phe Val Asn Phe Cys Glu Asp Thr Ile Phe Glu Met Gln Leu  
 4085 4090 4095  
 Ala Ser Gln Ile Ser Glu Ser Asp Ser Ala Asp Arg Pro Glu Glu  
 4100 4105 4110  
 Glu Glu Glu Asp Glu Asp Ser Ser Tyr Val Leu Glu Ile Ala Gly  
 4115 4120 4125  
 Glu Glu Glu Glu Asp Gly Ser Leu Glu Pro Ala Ser Ala Phe Ala  
 4130 4135 4140  
 Met Ala Cys Ala Ser Val Lys Arg Asn Val Thr Asp Phe Leu Lys  
 4145 4150 4155  
 Arg Ala Thr Leu Lys Asn Leu Arg Lys Gln Tyr Arg Asn Val Lys  
 4160 4165 4170  
 Lys Met Thr Ala Lys Glu Leu Val Lys Val Leu Phe Ser Phe Phe  
 4175 4180 4185  
 Trp Met Leu Phe Val Gly Leu Phe Gln Leu Leu Phe Thr Ile Leu  
 4190 4195 4200  
 Gly Gly Ile Phe Gln Ile Leu Trp Ser Thr Val Phe Gly Gly Gly  
 4205 4210 4215  
 Leu Val Glu Gly Ala Lys Asn Ile Arg Val Thr Lys Ile Leu Gly  
 4220 4225 4230

Asp Met Pro Asp Pro Thr Gln Phe Gly Ile His Asp Asp Thr Met  
 4235 4240 4245  
 Glu Ala Glu Arg Ala Glu Val Met Glu Pro Gly Ile Thr Thr Glu  
 4250 4255 4260  
 Leu Val His Phe Ile Lys Gly Glu Lys Gly Asp Thr Asp Ile Met  
 4265 4270 4275  
 Ser Asp Leu Phe Gly Leu His Pro Lys Lys Glu Gly Ser Leu Lys  
 4280 4285 4290  
 His Gly Pro Glu Val Gly Leu Gly Asp Leu Ser Glu Ile Ile Gly  
 4295 4300 4305  
 Lys Asp Glu Pro Pro Thr Leu Glu Ser Thr Val Gln Lys Lys Arg  
 4310 4315 4320  
 Lys Ala Gln Ala Ala Glu Met Lys Ala Ala Asn Glu Ala Glu Gly  
 4325 4330 4335  
 Lys Val Glu Ser Glu Lys Ala Asp Met Glu Asp Gly Glu Lys Glu  
 4340 4345 4350  
 Asp Lys Asp Lys Glu Glu Glu Gln Ala Glu Tyr Leu Trp Thr Glu  
 4355 4360 4365  
 Val Thr Lys Lys Lys Lys Arg Arg Cys Gly Gln Lys Val Glu Lys  
 4370 4375 4380  
 Pro Glu Ala Phe Thr Ala Asn Phe Phe Lys Gly Leu Glu Ile Tyr  
 4385 4390 4395  
 Gln Thr Lys Leu Leu His Tyr Leu Ala Arg Asn Phe Tyr Asn Leu  
 4400 4405 4410  
 Arg Phe Leu Ala Leu Phe Val Ala Phe Ala Ile Asn Phe Ile Leu  
 4415 4420 4425  
 Leu Phe Tyr Lys Val Thr Glu Glu Pro Leu Glu Glu Glu Thr Glu  
 4430 4435 4440  
 Asp Val Ala Asn Leu Trp Asn Ser Phe Asn Asp Glu Glu Glu Glu  
 4445 4450 4455  
 Glu Ala Met Val Phe Phe Val Leu Gln Glu Ser Thr Gly Tyr Met  
 4460 4465 4470



Ala Pro Thr Leu Arg Ala Leu Ala Ile Ile His Thr Ile Ile Ser  
 4475 4480 4485  
 Leu Val Cys Val Val Gly Tyr Tyr Cys Leu Lys Val Pro Leu Val  
 4490 4495 4500  
 Val Phe Lys Arg Glu Lys Glu Ile Ala Arg Lys Leu Glu Phe Asp  
 4505 4510 4515  
 Gly Leu Tyr Ile Thr Glu Gln Pro Ser Glu Asp Asp Ile Lys Gly  
 4520 4525 4530  
 Gln Trp Asp Arg Leu Val Ile Asn Thr Pro Ser Phe Pro Asn Asn  
 4535 4540 4545  
 Tyr Trp Asp Lys Phe Val Lys Arg Lys Val Ile Asn Lys Tyr Gly  
 4550 4555 4560  
 Asp Leu Tyr Gly Ala Glu Arg Ile Ala Glu Leu Leu Gly Leu Asp  
 4565 4570 4575  
 Lys Asn Ala Leu Asp Phe Ser Pro Val Glu Glu Thr Lys Ala Glu  
 4580 4585 4590  
 Ala Ala Ser Leu Val Ser Trp Leu Ser Ser Ile Asp Met Lys Tyr  
 4595 4600 4605  
 His Ile Trp Lys Leu Gly Val Val Phe Thr Asp Asn Ser Phe Leu  
 4610 4615 4620  
 Tyr Leu Ala Trp Tyr Thr Thr Met Ser Val Leu Gly His Tyr Asn  
 4625 4630 4635  
 Asn Phe Phe Phe Ala Ala His Leu Leu Asp Ile Ala Met Gly Phe  
 4640 4645 4650  
 Lys Thr Leu Arg Thr Ile Leu Ser Ser Val Thr His Asn Gly Lys  
 4655 4660 4665  
 Gln Leu Val Leu Thr Val Gly Leu Leu Ala Val Val Val Tyr Leu  
 4670 4675 4680  
 Tyr Thr Val Val Ala Phe Asn Phe Phe Arg Lys Phe Tyr Asn Lys  
 4685 4690 4695  
 Ser Glu Asp Asp Asp Glu Pro Asp Met Lys Cys Asp Asp Met Met  
 4700 4705 4710

Thr Cys Tyr Leu Phe His Met Tyr Val Gly Val Arg Ala Gly Gly  
 4715 4720 4725

Gly Ile Gly Asp Glu Ile Glu Asp Pro Ala Gly Asp Pro Tyr Glu  
 4730 4735 4740

Met Tyr Arg Ile Val Phe Asp Ile Thr Phe Phe Phe Phe Val Ile  
 4745 4750 4755

Val Ile Leu Leu Ala Ile Ile Gln Gly Leu Ile Ile Asp Ala Phe  
 4760 4765 4770

Gly Glu Leu Arg Asp Gln Gln Glu Gln Val Arg Glu Asp Met Glu  
 4775 4780 4785

Thr Lys Cys Phe Ile Cys Gly Ile Gly Asn Asp Tyr Phe Asp Thr  
 4790 4795 4800

Thr Pro His Gly Phe Glu Thr His Thr Leu Gln Glu His Asn Leu  
 4805 4810 4815

Ala Asn Tyr Leu Phe Phe Leu Met Tyr Leu Ile Asn Lys Asp Glu  
 4820 4825 4830

Thr Glu His Thr Gly Gln Glu Ser Tyr Val Trp Lys Met Tyr Gln  
 4835 4840 4845

Glu Arg Cys Trp Asp Phe Phe Pro Ala Gly Asp Cys Phe Arg Lys  
 4850 4855 4860

Gln Tyr Glu Asp Gln Leu Gly  
 4865 4870

<210> 145  
 <211> 1648  
 <212> PRT  
 <213> Homo sapiens

<400> 145

Met Ser Leu His Ser Thr His Asn Arg Asn Asn Ser Gly Asp Ile Leu  
 1 5 10 15

Asp Ile Pro Ser Ser Gln Asn Ser Ser Ser Leu Asn Ala Leu Thr His  
 20 25 30

Ser Ser Arg Leu Lys Leu His Leu Lys Ser Asp Met Ser Glu Cys Glu  
 35 40 45

Asn Asp Asp Pro Leu Leu Arg Ser Ala Gly Lys Val Arg Asp Ile Asn  
 50 55 60  
 Arg Thr Tyr Val Ile Ser Ala Ser Arg Lys Thr Ala Asp Met Pro Leu  
 65 70 75 80  
 Thr Pro Asn Pro Val Gly Arg Leu Ala Leu Gln Arg Arg Thr Thr Arg  
 85 90 95  
 Asn Lys Glu Ser Ser Leu Leu Val Ser Glu Leu Glu Asp Thr Thr Glu  
 100 105 110  
 Lys Thr Ala Glu Thr Arg Leu Thr Leu Gln Arg Arg Ala Lys Thr Asp  
 115 120 125  
 Ser Ala Glu Lys Trp Lys Thr Ala Glu Ile Asp Ser Val Lys Met Thr  
 130 135 140  
 Leu Asn Val Gly Gly Glu Thr Glu Asn Asn Gly Val Ser Lys Glu Ser  
 145 150 155 160  
 Arg Thr Asn Val Arg Ile Val Asn Asn Ala Lys Asn Ser Phe Val Ala  
 165 170 175  
 Ser Ser Val Pro Leu Asp Glu Asp Pro Gln Val Ile Glu Met Met Ala  
 180 185 190  
 Asp Lys Lys Tyr Lys Glu Thr Phe Ser Ala Pro Ser Arg Ala Asn Glu  
 195 200 205  
 Asn Val Ala Leu Lys Tyr Ser Ser Asn Arg Pro Pro Ile Ala Ser Leu  
 210 215 220  
 Ser Gln Thr Glu Val Val Arg Ser Gly His Leu Thr Thr Lys Pro Thr  
 225 230 235 240  
 Gln Ser Lys Leu Asp Ile Lys Val Leu Gly Thr Gly Asn Leu Tyr His  
 245 250 255  
 Arg Ser Ile Gly Lys Glu Ile Ala Lys Thr Ser Asn Lys Phe Gly Ser  
 260 265 270  
 Leu Glu Lys Arg Thr Pro Thr Lys Cys Thr Thr Glu His Lys Leu Thr  
 275 280 285  
 Thr Lys Cys Ser Leu Pro Gln Leu Lys Ser Pro Ala Pro Ser Ile Leu  
 290 295 300

Lys Asn Arg Met Ser Asn Leu Gln Val Lys Gln Arg Pro Lys Ser Ser  
 305 310 315 320  
 Phe Leu Ala Asn Lys Gln Glu Arg Ser Ala Glu Asn Thr Ile Leu Pro  
 325 330 335  
 Glu Glu Glu Thr Val Val Gln Asn Thr Ser Ala Gly Lys Asp Pro Leu  
 340 345 350  
 Lys Val Glu Asn Ser Gln Val Thr Val Ala Val Arg Val Arg Pro Phe  
 355 360 365  
 Thr Lys Arg Glu Lys Ile Glu Lys Ala Ser Gln Val Val Phe Met Ser  
 370 375 380  
 Gly Lys Glu Ile Thr Val Glu His Pro Asp Thr Lys Gln Val Tyr Asn  
 385 390 395 400  
 Phe Ile Tyr Asp Val Ser Phe Trp Ser Phe Asp Glu Cys His Pro His  
 405 410 415  
 Tyr Ala Ser Gln Thr Thr Val Tyr Glu Lys Leu Ala Ala Pro Leu Leu  
 420 425 430  
 Glu Arg Ala Phe Glu Gly Phe Asn Thr Cys Leu Phe Ala Tyr Gly Gln  
 435 440 445  
 Thr Gly Ser Gly Lys Ser Tyr Thr Met Met Gly Phe Ser Glu Glu Pro  
 450 455 460  
 Gly Ile Ile Pro Arg Phe Cys Glu Asp Leu Phe Ser Gln Val Ala Arg  
 465 470 475 480  
 Lys Gln Thr Gln Glu Val Ser Tyr His Ile Glu Met Ser Phe Phe Glu  
 485 490 495  
 Val Tyr Asn Glu Lys Ile His Asp Leu Leu Val Cys Lys Asp Glu Asn  
 500 505 510  
 Gly Gln Arg Lys Gln Pro Leu Arg Val Arg Glu His Pro Val Tyr Gly  
 515 520 525  
 Pro Tyr Val Glu Ala Leu Ser Met Asn Ile Val Ser Ser Tyr Ala Asp  
 530 535 540  
 Ile Gln Ser Trp Leu Glu Leu Gly Asn Lys Gln Arg Ala Thr Ala Ala  
 545 550 555 560

Thr Gly Met Asn Asp Lys Ser Ser Arg Ser His Ser Val Phe Thr Leu  
 565 570 575  
 Val Met Thr Gln Thr Lys Thr Glu Phe Val Glu Gly Glu Glu His Asp  
 580 585 590  
 His Arg Ile Thr Ser Arg Ile Asn Leu Ile Asp Leu Ala Gly Ser Glu  
 595 600 605  
 Arg Cys Ser Thr Ala His Thr Asn Gly Asp Arg Leu Lys Glu Gly Val  
 610 615 620  
 Ser Ile Asn Lys Ser Leu Leu Thr Leu Gly Lys Val Ile Ser Ala Leu  
 625 630 635 640  
 Ser Glu Gln Ala Asn Gln Arg Ser Val Phe Ile Pro Tyr Arg Glu Ser  
 645 650 655  
 Val Leu Thr Trp Leu Leu Lys Glu Ser Leu Gly Gly Asn Ser Lys Thr  
 660 665 670  
 Ala Met Ile Ala Thr Ile Ser Pro Ala Ala Ser Asn Ile Glu Glu Thr  
 675 680 685  
 Leu Ser Thr Leu Arg Tyr Ala Asn Gln Ala Arg Leu Ile Val Asn Ile  
 690 695 700  
 Ala Lys Val Asn Glu Asp Met Asn Ala Lys Leu Ile Arg Glu Leu Lys  
 705 710 715 720  
 Ala Glu Ile Ala Lys Leu Lys Ala Ala Gln Arg Asn Ser Arg Asn Ile  
 725 730 735  
 Asp Pro Glu Arg Tyr Arg Leu Cys Arg Gln Glu Ile Thr Ser Leu Arg  
 740 745 750  
 Met Lys Leu His Gln Gln Glu Arg Asp Met Ala Glu Met Gln Arg Val  
 755 760 765  
 Trp Lys Glu Lys Phe Glu Gln Ala Glu Lys Arg Lys Leu Gln Glu Thr  
 770 775 780  
 Lys Glu Leu Gln Lys Ala Gly Ile Met Phe Gln Met Asp Asn His Leu  
 785 790 795 800  
 Pro Asn Leu Val Asn Leu Asn Glu Asp Pro Gln Leu Ser Glu Met Leu  
 805 810 815

Leu Tyr Met Ile Lys Glu Gly Thr Thr Thr Val Gly Lys Tyr Lys Pro  
820 825 830

Asn Ser Ser His Asp Ile Gln Leu Ser Gly Val Leu Ile Ala Asp Asp  
835 840 845

His Cys Thr Ile Lys Asn Phe Gly Gly Thr Val Ser Ile Ile Pro Val  
850 855 860

Gly Glu Ala Lys Thr Tyr Val Asn Gly Lys His Ile Leu Glu Ile Thr  
865 870 875 880

Val Leu Arg His Gly Asp Arg Val Ile Leu Gly Gly Asp His Tyr Phe  
885 890 895

Arg Phe Asn His Pro Val Glu Val Gln Lys Gly Lys Arg Pro Ser Gly  
900 905 910

Arg Asp Thr Pro Ile Ser Glu Gly Pro Lys Asp Phe Glu Phe Ala Lys  
915 920 925

Asn Glu Leu Leu Met Ala Gln Arg Ser Gln Leu Glu Ala Glu Ile Lys  
930 935 940

Glu Ala Gln Leu Lys Ala Lys Glu Glu Met Met Gln Gly Ile Gln Ile  
945 950 955 960

Ala Lys Glu Met Ala Gln Gln Glu Leu Ser Ser Gln Lys Ala Ala Tyr  
965 970 975

Glu Ser Lys Ile Lys Ala Leu Glu Ala Glu Leu Arg Glu Glu Ser Gln  
980 985 990

Arg Lys Lys Met Gln Glu Ile Asn Asn Gln Lys Ala Asn His Lys Ile  
995 1000 1005

Glu Glu Leu Glu Lys Ala Lys Gln His Leu Glu Gln Glu Ile Tyr  
1010 1015 1020

Val Asn Lys Lys Arg Leu Glu Met Glu Thr Leu Ala Thr Lys Gln  
1025 1030 1035

Ala Leu Glu Asp His Ser Ile Arg His Ala Arg Ile Leu Glu Ala  
1040 1045 1050

Leu Glu Thr Glu Lys Gln Lys Ile Ala Lys Glu Val Gln Ile Leu  
1055 1060 1065

Gln Gln Asn Arg Asn Asn Arg Asp Lys Thr Phe Thr Val Gln Thr  
 1070 1075 1080  
 Thr Trp Ser Ser Met Lys Leu Ser Met Met Ile Gln Glu Ala Asn  
 1085 1090 1095  
 Ala Ile Ser Ser Lys Leu Lys Thr Tyr Tyr Val Phe Gly Arg His  
 1100 1105 1110  
 Asp Ile Ser Asp Lys Ser Ser Ser Asp Thr Ser Ile Arg Val Arg  
 1115 1120 1125  
 Asn Leu Lys Leu Gly Ile Ser Thr Phe Trp Ser Leu Glu Lys Phe  
 1130 1135 1140  
 Glu Ser Lys Leu Ala Ala Met Lys Glu Leu Tyr Glu Ser Asn Gly  
 1145 1150 1155  
 Ser Asn Arg Gly Glu Asp Ala Phe Cys Asp Pro Glu Asp Glu Trp  
 1160 1165 1170  
 Glu Pro Asp Ile Thr Asp Ala Pro Val Ser Ser Leu Ser Arg Arg  
 1175 1180 1185  
 Arg Ser Arg Ser Leu Met Lys Asn Arg Arg Ile Ser Gly Cys Leu  
 1190 1195 1200  
 His Asp Ile Gln Val His Pro Ile Lys Asn Leu His Ser Ser His  
 1205 1210 1215  
 Ser Ser Gly Leu Met Asp Lys Ser Ser Thr Ile Tyr Ser Asn Ser  
 1220 1225 1230  
 Ala Glu Ser Phe Leu Pro Gly Ile Cys Lys Glu Leu Ile Gly Ser  
 1235 1240 1245  
 Ser Leu Asp Phe Phe Gly Gln Ser Tyr Asp Glu Glu Arg Thr Ile  
 1250 1255 1260  
 Ala Asp Ser Leu Ile Asn Ser Phe Leu Lys Ile Tyr Asn Gly Leu  
 1265 1270 1275  
 Phe Ala Ile Ser Lys Ala His Glu Glu Gln Asp Glu Glu Ser Gln  
 1280 1285 1290  
 Asp Asn Leu Phe Ser Ser Asp Arg Ala Ile Gln Ser Leu Thr Ile  
 1295 1300 1305

Gln Thr Ala Cys Ala Phe Glu Gln Leu Val Val Leu Met Lys His  
 1310 1315 1320  
 Trp Leu Ser Asp Leu Leu Pro Cys Thr Asn Ile Ala Arg Leu Glu  
 1325 1330 1335  
 Asp Glu Leu Arg Gln Glu Val Lys Lys Leu Gly Gly Tyr Leu Gln  
 1340 1345 1350  
 Leu Phe Leu Gln Gly Cys Cys Leu Asp Ile Ser Ser Met Ile Lys  
 1355 1360 1365  
 Glu Ala Gln Lys Asn Ala Ile Gln Ile Val Gln Gln Ala Val Lys  
 1370 1375 1380  
 Tyr Val Gly Gln Leu Ala Val Leu Lys Gly Ser Lys Leu His Phe  
 1385 1390 1395  
 Leu Glu Asn Gly Asn Asn Lys Ala Ala Ser Val Gln Glu Glu Phe  
 1400 1405 1410  
 Met Asp Ala Val Cys Asp Gly Val Gly Leu Gly Met Lys Ile Leu  
 1415 1420 1425  
 Leu Asp Ser Gly Leu Glu Lys Ala Lys Glu Leu Gln His Glu Leu  
 1430 1435 1440  
 Phe Arg Gln Cys Thr Lys Asn Glu Val Thr Lys Glu Met Lys Thr  
 1445 1450 1455  
 Asn Ala Met Gly Leu Ile Arg Ser Leu Glu Asn Ile Phe Ala Glu  
 1460 1465 1470  
 Ser Lys Ile Lys Ser Phe Arg Arg Gln Val Gln Glu Glu Asn Phe  
 1475 1480 1485  
 Glu Tyr Gln Asp Phe Lys Arg Met Val Asn Arg Ala Pro Glu Phe  
 1490 1495 1500  
 Leu Lys Leu Lys His Cys Leu Glu Lys Ala Ile Glu Ile Ile Ile  
 1505 1510 1515  
 Ser Ala Leu Lys Gly Cys His Ser Asp Ile Asn Leu Leu Gln Thr  
 1520 1525 1530  
 Cys Val Glu Ser Ile Arg Asn Leu Ala Ser Asp Phe Tyr Ser Asp  
 1535 1540 1545



Phe Ser Val Pro Ser Thr Ser Val Gly Ser Tyr Glu Ser Arg Val  
1550 1555 1560

Thr His Ile Val His Gln Glu Leu Glu Ser Leu Ala Lys Ser Leu  
1565 1570 1575

Leu Phe Cys Phe Glu Ser Glu Glu Ser Pro Asp Leu Leu Lys Pro  
1580 1585 1590

Trp Glu Thr Tyr Asn Gln Asn Thr Lys Glu Glu His Gln Gln Ser  
1595 1600 1605

Lys Ser Ser Gly Ile Asp Gly Ser Lys Asn Lys Gly Val Pro Lys  
1610 1615 1620

Arg Val Tyr Glu Leu His Gly Ser Ser Pro Ala Val Ser Ser Glu  
1625 1630 1635

Glu Cys Thr Pro Ser Arg Ile Gln Trp Val  
1640 1645

<210> 146  
<211> 270  
<212> PRT  
<213> Homo sapiens

<400> 146

Met Trp Leu Leu Val Ser Val Ile Leu Ile Ser Arg Ile Ser Ser Val  
1 5 10 15

Gly Gly Glu Ala Met Phe Cys Asp Phe Pro Lys Ile Asn His Gly Ile  
20 25 30

Leu Tyr Asp Glu Glu Lys Tyr Lys Pro Phe Ser Gln Val Pro Thr Gly  
35 40 45

Glu Val Phe Tyr Tyr Ser Cys Glu Tyr Asn Phe Val Ser Pro Ser Lys  
50 55 60

Ser Phe Trp Thr Arg Ile Thr Cys Ala Glu Glu Gly Trp Ser Pro Thr  
65 70 75 80

Pro Lys Cys Leu Arg Leu Cys Phe Phe Pro Phe Val Glu Asn Gly His  
85 90 95

Ser Glu Ser Ser Gly Gln Thr His Leu Glu Gly Asp Thr Val Gln Ile  
100 105 110

Ile Cys Asn Thr Gly Tyr Arg Leu Gln Asn Asn Glu Asn Asn Ile Ser

115 120 125  
 Cys Val Glu Arg Gly Trp Ser Thr Pro Pro Lys Cys Arg Ser Thr Ile  
 130 135 140  
 Ser Ala Glu Lys Cys Gly Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile  
 145 150 155 160  
 Thr Ser Phe Leu Leu Ser Val Tyr Ala Pro Gly Ser Ser Val Glu Tyr  
 165 170 175  
 Gln Cys Gln Asn Leu Tyr Gln Leu Glu Gly Asn Asn Gln Ile Thr Cys  
 180 185 190  
 Arg Asn Gly Gln Trp Ser Glu Pro Pro Lys Cys Leu Asp Pro Cys Val  
 195 200 205  
 Ile Ser Gln Glu Ile Met Glu Lys Tyr Asn Ile Lys Leu Lys Trp Thr  
 210 215 220  
 Asn Gln Gln Lys Leu Tyr Ser Arg Thr Gly Asp Ile Val Glu Phe Val  
 225 230 235 240  
 Cys Lys Ser Gly Tyr His Pro Thr Lys Ser His Ser Phe Arg Ala Met  
 245 250 255  
 Cys Gln Asn Gly Lys Leu Val Tyr Pro Ser Cys Glu Glu Lys  
 260 265 270  
 <210> 147  
 <211> 244  
 <212> PRT  
 <213> Homo sapiens  
 <400> 147  
 Met Glu Leu Thr Ile Phe Ile Leu Arg Leu Ala Ile Tyr Ile Leu Thr  
 1 5 10 15  
 Phe Pro Leu Tyr Leu Leu Asn Phe Leu Gly Leu Trp Ser Trp Ile Cys  
 20 25 30  
 Lys Lys Trp Phe Pro Tyr Leu Leu Val Arg Phe Thr Val Ile Tyr Asn  
 35 40 45  
 Glu Gln Met Ala Ser Lys Lys Arg Glu Leu Phe Ser Asn Leu Gln Glu  
 50 55 60  
 Phe Ala Gly Pro Ser Gly Lys Leu Ser Leu Leu Glu Val Gly Cys Gly  
 65 70 75 80

Thr Gly Ala Asn Phe Lys Phe Tyr Pro Pro Gly Cys Arg Val Thr Cys  
85 90 95

Ile Asp Pro Asn Pro Asn Phe Glu Lys Phe Leu Ile Lys Ser Ile Ala  
100 105 110

Glu Asn Arg His Leu Gln Phe Glu Arg Phe Val Val Ala Ala Gly Glu  
115 120 125

Asn Met His Gln Val Ala Asp Gly Ser Val Asp Val Val Val Cys Thr  
130 135 140

Leu Val Leu Cys Ser Val Lys Asn Gln Glu Arg Ile Leu Arg Glu Val  
145 150 155 160

Cys Arg Val Leu Arg Pro Gly Gly Ala Phe Tyr Phe Met Glu His Val  
165 170 175

Ala Ala Glu Cys Ser Thr Trp Asn Tyr Phe Trp Gln Gln Val Leu Asp  
180 185 190

Pro Ala Trp His Leu Leu Phe Asp Gly Cys Asn Leu Thr Arg Glu Ser  
195 200 205

Trp Lys Ala Leu Glu Arg Ala Ser Phe Ser Lys Leu Lys Leu Gln His  
210 215 220

Ile Gln Ala Pro Leu Ser Trp Glu Leu Val Arg Pro His Ile Tyr Gly  
225 230 235 240

Tyr Ala Val Lys

<210> 148  
<211> 558  
<212> PRT  
<213> Homo sapiens

<400> 148

Met Ala Ala Leu Thr Arg Asp Pro Gln Phe Gln Lys Leu Gln Gln Trp  
1 5 10 15

Tyr Arg Glu His Arg Ser Glu Leu Asn Leu Arg Arg Leu Phe Asp Ala  
20 25 30

Asn Lys Asp Arg Phe Asn His Phe Ser Leu Thr Leu Asn Thr Asn His  
35 40 45

Gly His Ile Leu Val Asp Tyr Ser Lys Asn Leu Val Thr Glu Asp Val  
 50 55 60  
 Met Arg Met Leu Val Asp Leu Ala Lys Ser Arg Gly Val Glu Ala Ala  
 65 70 75 80  
 Arg Glu Arg Met Phe Asn Gly Glu Lys Ile Asn Tyr Thr Glu Gly Arg  
 85 90 95  
 Ala Val Leu His Val Ala Leu Arg Asn Arg Ser Asn Thr Pro Ile Leu  
 100 105 110  
 Val Asp Gly Lys Asp Val Met Pro Glu Val Asn Lys Val Leu Asp Lys  
 115 120 125  
 Met Lys Ser Phe Cys Gln Arg Val Arg Ser Gly Asp Trp Lys Gly Tyr  
 130 135 140  
 Thr Gly Lys Thr Ile Thr Asp Val Ile Asn Ile Gly Ile Gly Gly Ser  
 145 150 155 160  
 Asp Leu Gly Pro Leu Met Val Thr Glu Ala Leu Lys Pro Tyr Ser Ser  
 165 170 175  
 Gly Gly Pro Arg Val Trp Tyr Val Ser Asn Ile Asp Gly Thr His Ile  
 180 185 190  
 Ala Lys Thr Leu Ala Gln Leu Asn Pro Glu Ser Ser Leu Phe Ile Ile  
 195 200 205  
 Ala Ser Lys Thr Phe Thr Thr Gln Glu Thr Ile Thr Asn Ala Glu Thr  
 210 215 220  
 Ala Lys Glu Trp Phe Leu Gln Ala Ala Lys Asp Pro Ser Ala Val Ala  
 225 230 235 240  
 Lys His Phe Val Ala Leu Ser Thr Asn Thr Thr Lys Val Lys Glu Phe  
 245 250 255  
 Gly Ile Asp Pro Gln Asn Met Phe Glu Phe Trp Asp Trp Val Gly Gly  
 260 265 270  
 Arg Tyr Ser Leu Trp Ser Ala Ile Gly Leu Ser Ile Ala Leu His Val  
 275 280 285  
 Gly Phe Asp Asn Phe Glu Gln Leu Leu Ser Gly Ala His Trp Met Asp  
 290 295 300

Gln His Phe Arg Thr Thr Pro Leu Glu Lys Asn Ala Pro Val Leu Leu  
 305 310 315 320  
 Ala Leu Leu Gly Ile Trp Tyr Ile Asn Cys Phe Gly Cys Glu Thr His  
 325 330 335  
 Ala Met Leu Pro Tyr Asp Gln Tyr Leu His Arg Phe Ala Ala Tyr Phe  
 340 345 350  
 Gln Gln Gly Asp Met Glu Ser Asn Gly Lys Tyr Ile Thr Lys Ser Gly  
 355 360 365  
 Thr Arg Val Asp His Gln Thr Gly Pro Ile Val Trp Gly Glu Pro Gly  
 370 375 380  
 Thr Asn Gly Gln His Ala Phe Tyr Gln Leu Ile His Gln Gly Thr Lys  
 385 390 395 400  
 Met Ile Pro Cys Asp Phe Leu Ile Pro Val Gln Thr Gln His Pro Ile  
 405 410 415  
 Arg Lys Gly Leu His His Lys Ile Leu Leu Ala Asn Phe Leu Ala Gln  
 420 425 430  
 Thr Glu Ala Leu Met Arg Gly Lys Ser Thr Glu Glu Ala Arg Lys Glu  
 435 440 445  
 Leu Gln Ala Ala Gly Lys Ser Pro Glu Asp Leu Glu Arg Leu Leu Pro  
 450 455 460  
 His Lys Val Phe Glu Gly Asn Arg Pro Thr Asn Ser Ile Val Phe Thr  
 465 470 475 480  
 Lys Leu Thr Pro Phe Met Leu Gly Ala Leu Val Ala Met Tyr Glu His  
 485 490 495  
 Lys Ile Phe Val Gln Gly Ile Ile Trp Asp Ile Asn Ser Phe Asp Gln  
 500 505 510  
 Trp Gly Val Glu Leu Gly Lys Gln Leu Ala Lys Lys Ile Glu Pro Glu  
 515 520 525  
 Leu Asp Gly Ser Ala Gln Val Thr Ser His Asp Ala Ser Thr Asn Gly  
 530 535 540  
 Leu Ile Asn Phe Ile Lys Gln Gln Arg Glu Ala Arg Val Gln  
 545 550 555

<210> 149  
 <211> 184  
 <212> PRT  
 <213> Homo sapiens

<400> 149

Met Lys Ser Val Leu Leu Leu Thr Thr Leu Leu Val Pro Ala His Leu  
 1 5 10 15

Val Ala Ala Trp Ser Asn Asn Tyr Ala Val Asp Cys Pro Gln His Cys  
 20 25 30

Asp Ser Ser Glu Cys Lys Ser Ser Pro Arg Cys Lys Arg Thr Val Leu  
 35 40 45

Asp Asp Cys Gly Cys Cys Arg Val Cys Ala Ala Gly Arg Gly Glu Thr  
 50 55 60

Cys Tyr Arg Thr Val Ser Gly Met Asp Gly Met Lys Cys Gly Pro Gly  
 65 70 75 80

Leu Arg Cys Gln Pro Ser Asn Gly Glu Asp Pro Phe Gly Glu Glu Phe  
 85 90 95

Gly Ile Cys Lys Asp Cys Pro Tyr Gly Thr Phe Gly Met Asp Cys Arg  
 100 105 110

Glu Thr Cys Asn Cys Gln Ser Gly Ile Cys Asp Arg Gly Thr Gly Lys  
 115 120 125

Cys Leu Lys Phe Pro Phe Phe Gln Tyr Ser Val Thr Lys Ser Ser Asn  
 130 135 140

Arg Phe Val Ser Leu Thr Glu His Asp Met Ala Ser Gly Asp Gly Asn  
 145 150 155 160

Ile Val Arg Glu Glu Val Val Lys Glu Asn Ala Ala Gly Ser Pro Val  
 165 170 175

Met Arg Lys Trp Leu Asn Pro Arg  
 180

<210> 150  
 <211> 199  
 <212> PRT  
 <213> Homo sapiens

<400> 150

Met Ser Ser Gly Asn Ala Lys Ile Gly His Pro Ala Pro Asn Phe Lys

399/514

Glu Glu Asp Gly Lys Thr Lys Gly Tyr Ile Phe Leu Glu Tyr Ala Ser  
 35 40 45  
 Pro Ala His Ala Val Asp Ala Val Lys Asn Ala Asp Gly Tyr Lys Leu  
 50 55 60  
 Asp Lys Gln His Thr Phe Arg Val Asn Leu Phe Thr Asp Phe Asp Lys  
 65 70 75 80  
 Tyr Met Thr Ile Ser Asp Glu Trp Asp Ile Pro Glu Lys Gln Pro Phe  
 85 90 95  
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 Cys Glu Arg Tyr Leu Val Thr Phe Ser Pro Leu Met Asp Thr Gln Asp  
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 Asp Pro Gln Ala Ile Ile Ile Trp Asp Ile Leu Thr Gly His Lys Lys  
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 Arg Gly Phe His Cys Glu Ser Ser Ala His Trp Pro Ile Phe Lys Trp  
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<212> PRT  
<213> Homo sapiens

<400> 152

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Gln Leu Ile Arg Gly Leu Gly Gln Glu Cys Val Leu Ser Ser Ser Pro  
35 40 45

Ala Val Leu Ala Leu Gln Thr Ser Leu Val Phe Ser Arg Asp Phe Gly  
50 55 60

Leu Leu Val Phe Val Arg Lys Ser Leu Asn Ser Ile Glu Phe Arg Glu  
65 70 75 80

Cys Arg Glu Glu Ile Leu Lys Phe Leu Cys Ile Phe Leu Glu Lys Met  
85 90 95

Gly Gln Lys Ile Ala Pro Tyr Ser Val Glu Ile Lys Asn Thr Cys Thr  
100 105 110

Ser Val Tyr Thr Lys Asp Arg Ala Ala Lys Cys Lys Ile Pro Ala Leu  
115 120 125

Asp Leu Leu Ile Lys Leu Leu Gln Thr Phe Arg Ser Ser Arg Leu Met  
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Val Ala Ser Val Leu Leu Tyr Leu Asp Thr Val Pro Glu Val Tyr Thr  
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Tyr Ser Pro Lys Met Gln Leu Val Cys Cys Arg Ala Ile Val Lys Val  
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Ser Thr Arg Leu Pro Leu Ile Ser Gly Phe Tyr Lys Leu Leu Ser Ile  
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 Thr Val Arg Asn Ala Lys Lys Ile Lys Tyr Phe Glu Gly Val Ser Pro  
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Val Met Tyr Ser Arg Leu Pro Lys Asp Asp Val His Ala Lys Glu  
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 Leu Gln Ile Ile Glu Arg Tyr Pro Glu Glu Thr Leu Ser Leu Met  
 3470 3475 3480  
 Thr Lys Glu Ile Ser Ser Val Pro Cys Trp Gln Phe Ile Ser Trp  
 3485 3490 3495  
 Ile Ser His Met Val Ala Leu Leu Asp Lys Asp Gln Ala Val Ala  
 3500 3505 3510  
 Val Gln His Ser Val Glu Glu Ile Thr Asp Asn Tyr Pro Gln Ala  
 3515 3520 3525  
 Ile Val Tyr Pro Phe Ile Ile Ser Ser Glu Ser Tyr Ser Phe Lys  
 3530 3535 3540  
 Asp Thr Ser Thr Gly His Lys Asn Lys Glu Phe Val Ala Arg Ile  
 3545 3550 3555



Lys Ser Lys Leu Asp Gln Gly Gly Val Ile Gln Asp Phe Ile Asn  
 3560 3565 3570  
 Ala Leu Asp Gln Leu Ser Asn Pro Glu Leu Leu Phe Lys Asp Trp  
 3575 3580 3585  
 Ser Asn Asp Val Arg Ala Glu Leu Ala Lys Thr Pro Val Asn Lys  
 3590 3595 3600  
 Lys Asn Ile Glu Lys Met Tyr Glu Arg Met Tyr Ala Ala Leu Gly  
 3605 3610 3615  
 Asp Pro Lys Ala Pro Gly Leu Gly Ala Phe Arg Arg Lys Phe Ile  
 3620 3625 3630  
 Gln Thr Phe Gly Lys Glu Phe Asp Lys His Phe Gly Lys Gly Gly  
 3635 3640 3645  
 Ser Lys Leu Leu Arg Met Lys Leu Ser Asp Phe Asn Asp Ile Thr  
 3650 3655 3660  
 Asn Met Leu Leu Leu Lys Met Asn Lys Asp Ser Lys Pro Pro Gly  
 3665 3670 3675  
 Asn Leu Lys Glu Cys Ser Pro Trp Met Ser Asp Phe Lys Val Glu  
 3680 3685 3690  
 Phe Leu Arg Asn Glu Leu Glu Ile Pro Gly Gln Tyr Asp Gly Arg  
 3695 3700 3705  
 Gly Lys Pro Leu Pro Glu Tyr His Val Arg Ile Ala Gly Phe Asp  
 3710 3715 3720  
 Glu Arg Val Thr Val Met Ala Ser Leu Arg Arg Pro Lys Arg Ile  
 3725 3730 3735  
 Ile Ile Arg Gly His Asp Glu Arg Glu His Pro Phe Leu Val Lys  
 3740 3745 3750  
 Gly Gly Glu Asp Leu Arg Gln Asp Gln Arg Val Glu Gln Leu Phe  
 3755 3760 3765  
 Gln Val Met Asn Gly Ile Leu Ala Gln Asp Ser Ala Cys Ser Gln  
 3770 3775 3780  
 Arg Ala Leu Gln Leu Arg Thr Tyr Ser Val Val Pro Met Thr Ser  
 3785 3790 3795

Arg Leu Gly Leu Ile Glu Trp Leu Glu Asn Thr Val Thr Leu Lys  
 3800 3805 3810  
 Asp Leu Leu Leu Asn Thr Met Ser Gln Glu Glu Lys Ala Ala Tyr  
 3815 3820 3825  
 Leu Ser Asp Pro Arg Ala Pro Pro Cys Glu Tyr Lys Asp Trp Leu  
 3830 3835 3840  
 Thr Lys Met Ser Gly Lys His Asp Val Gly Ala Tyr Met Leu Met  
 3845 3850 3855  
 Tyr Lys Gly Ala Asn Arg Thr Glu Thr Val Thr Ser Phe Arg Lys  
 3860 3865 3870  
 Arg Glu Ser Lys Val Pro Ala Asp Leu Leu Lys Arg Ala Phe Val  
 3875 3880 3885  
 Arg Met Ser Thr Ser Pro Glu Ala Phe Leu Ala Leu Arg Ser His  
 3890 3895 3900  
 Phe Ala Ser Ser His Ala Leu Ile Cys Ile Ser His Trp Ile Leu  
 3905 3910 3915  
 Gly Ile Gly Asp Arg His Leu Asn Asn Phe Met Val Ala Met Glu  
 3920 3925 3930  
 Thr Gly Gly Val Ile Gly Ile Asp Phe Gly His Ala Phe Gly Ser  
 3935 3940 3945  
 Ala Thr Gln Phe Leu Pro Val Pro Glu Leu Met Pro Phe Arg Leu  
 3950 3955 3960  
 Thr Arg Gln Phe Ile Asn Leu Met Leu Pro Met Lys Glu Thr Gly  
 3965 3970 3975  
 Leu Met Tyr Ser Ile Met Val His Ala Leu Arg Ala Phe Arg Ser  
 3980 3985 3990  
 Asp Pro Gly Leu Leu Thr Asn Thr Met Asp Val Phe Val Lys Glu  
 3995 4000 4005  
 Pro Ser Phe Asp Trp Lys Asn Phe Glu Gln Lys Met Leu Lys Lys  
 4010 4015 4020  
 Gly Gly Ser Trp Ile Gln Glu Ile Asn Val Ala Glu Lys Asn Trp  
 4025 4030 4035

Tyr Pro Arg Gln Lys Ile Cys Tyr Ala Lys Arg Lys Leu Ala Gly  
4040 4045 4050

Ala Asn Pro Ala Val Ile Thr Cys Asp Glu Leu Leu Leu Gly His  
4055 4060 4065

Glu Lys Ala Pro Ala Phe Arg Asp Tyr Val Ala Val Ala Arg Gly  
4070 4075 4080

Ser Lys Asp His Asn Ile Arg Ala Gln Glu Pro Glu Ser Gly Leu  
4085 4090 4095

Ser Glu Glu Thr Gln Val Lys Cys Leu Met Asp Gln Ala Thr Asp  
4100 4105 4110

Pro Asn Ile Leu Gly Arg Thr Trp Glu Gly Trp Glu Pro Trp Met  
4115 4120 4125

<210> 153  
<211> 295  
<212> PRT  
<213> Homo sapiens

<400> 153

Met Glu His Gln Leu Leu Cys Cys Glu Val Glu Thr Ile Arg Arg Ala  
1 5 10 15

Tyr Pro Asp Ala Asn Leu Leu Asn Asp Arg Val Leu Arg Ala Met Leu  
20 25 30

Lys Ala Glu Glu Thr Cys Ala Pro Ser Val Ser Tyr Phe Lys Cys Val  
35 40 45

Gln Lys Glu Val Leu Pro Ser Met Arg Lys Ile Val Ala Thr Trp Met  
50 55 60

Leu Glu Val Cys Glu Glu Gln Lys Cys Glu Glu Glu Val Phe Pro Leu  
65 70 75 80

Ala Met Asn Tyr Leu Asp Arg Phe Leu Ser Leu Glu Pro Val Lys Lys  
85 90 95

Ser Arg Leu Gln Leu Leu Gly Ala Thr Cys Met Phe Val Ala Ser Lys  
100 105 110

Met Lys Glu Thr Ile Pro Leu Thr Ala Glu Lys Leu Cys Ile Tyr Thr  
115 120 125

Asp Asn Ser Ile Arg Pro Glu Glu Leu Leu Gln Met Glu Leu Leu Leu  
130 135 140

Val Asn Lys Leu Lys Trp Asn Leu Ala Ala Met Thr Pro His Asp Phe  
145 150 155 160

Ile Glu His Phe Leu Ser Lys Met Pro Glu Ala Glu Glu Asn Lys Gln  
165 170 175

Ile Ile Arg Lys His Ala Gln Thr Phe Val Ala Leu Cys Ala Thr Asp  
180 185 190

Val Lys Phe Ile Ser Asn Pro Pro Ser Met Val Ala Ala Gly Ser Val  
195 200 205

Val Ala Ala Val Gln Gly Leu Asn Leu Arg Ser Pro Asn Asn Phe Leu  
210 215 220

Ser Tyr Tyr Arg Leu Thr Arg Phe Leu Ser Arg Val Ile Lys Cys Asp  
225 230 235 240

Pro Asp Cys Leu Arg Ala Cys Gln Glu Gln Ile Glu Ala Leu Leu Glu  
245 250 255

Ser Ser Leu Arg Gln Ala Gln Gln Asn Met Asp Pro Lys Ala Ala Glu  
260 265 270

Glu Glu Glu Glu Glu Glu Glu Val Asp Leu Ala Cys Thr Pro Thr  
275 280 285

Asp Val Arg Asp Val Asp Ile  
290 295

<210> 154  
<211> 856  
<212> PRT  
<213> Homo sapiens

<400> 154

Met Asp Val Arg Arg Leu Lys Val Asn Glu Leu Arg Glu Glu Leu Gln  
1 5 10 15

Arg Arg Gly Leu Asp Thr Arg Gly Leu Lys Thr Glu Leu Ala Glu Arg  
20 25 30

Leu Gln Ala Ala Leu Glu Ala Glu Glu Pro Asp Asp Glu Arg Glu Leu  
35 40 45

Asp Ala Asp Asp Glu Pro Gly Arg Pro Gly His Ile Asn Glu Glu Val

50                                      55                                      60  
 Glu Thr Glu Gly Gly Ser Glu Leu Glu Gly Thr Ala Gln Pro Pro Pro  
 65                                      70                                      75  
 Pro Gly Leu Gln Pro His Ala Glu Pro Gly Gly Tyr Ser Gly Pro Asp  
 85                                      90                                      95  
 Gly His Tyr Ala Met Asp Asn Ile Thr Arg Gln Asn Gln Phe Tyr Asp  
 100                                      105                                      110  
 Thr Gln Val Ile Lys Gln Glu Asn Glu Ser Gly Tyr Glu Arg Arg Pro  
 115                                      120                                      125  
 Leu Glu Met Glu Gln Gln Gln Ala Tyr Arg Pro Glu Met Lys Thr Glu  
 130                                      135                                      140  
 Met Lys Gln Gly Ala Pro Thr Ser Phe Leu Pro Pro Glu Ala Ser Gln  
 145                                      150                                      155                                      160  
 Leu Lys Pro Asp Arg Gln Gln Phe Gln Ser Arg Lys Arg Pro Tyr Glu  
 165                                      170                                      175  
 Glu Asn Arg Gly Arg Gly Tyr Phe Glu His Arg Glu Asp Arg Arg Gly  
 180                                      185                                      190  
 Arg Ser Pro Gln Pro Pro Ala Glu Glu Asp Glu Asp Asp Phe Asp Asp  
 195                                      200                                      205  
 Thr Leu Val Ala Ile Asp Thr Tyr Asn Cys Asp Leu His Phe Lys Val  
 210                                      215                                      220  
 Ala Arg Asp Arg Ser Ser Gly Tyr Pro Leu Thr Ile Glu Gly Phe Ala  
 225                                      230                                      235                                      240  
 Tyr Leu Trp Ser Gly Ala Arg Ala Ser Tyr Gly Val Arg Arg Gly Arg  
 245                                      250                                      255  
 Val Cys Phe Glu Met Lys Ile Asn Glu Glu Ile Ser Val Lys His Leu  
 260                                      265                                      270  
 Pro Ser Thr Glu Pro Asp Pro His Val Val Arg Ile Gly Trp Ser Leu  
 275                                      280                                      285  
 Asp Ser Cys Ser Thr Gln Leu Gly Glu Glu Pro Phe Ser Tyr Gly Tyr  
 290                                      295                                      300  
 Gly Gly Thr Gly Lys Lys Ser Thr Asn Ser Arg Phe Glu Asn Tyr Gly

305                      310                      315                      320  
 Asp Lys Phe Ala Glu Asn Asp Val Ile Gly Cys Phe Ala Asp Phe Glu  
                                  325                                   330                                   335  
 Cys Gly Asn Asp Val Glu Leu Ser Phe Thr Lys Asn Gly Lys Trp Met  
                                  340                                   345                                   350  
 Gly Ile Ala Phe Arg Ile Gln Lys Glu Ala Leu Gly Gly Gln Ala Leu  
                                  355                                   360                                   365  
 Tyr Pro His Val Leu Val Lys Asn Cys Ala Val Glu Phe Asn Phe Gly  
                                  370                                   375                                   380  
 Gln Arg Ala Glu Pro Tyr Cys Ser Val Leu Pro Gly Phe Thr Phe Ile  
                                  385                                   390                                   395                                   400  
 Gln His Leu Pro Leu Ser Glu Arg Ile Arg Gly Thr Val Gly Pro Lys  
    405     410     415  
 Ser Lys Ala Glu Cys Glu Ile Leu Met Met Val Gly Leu Pro Ala Ala  
    420     425     430  
 Gly Lys Thr Thr Trp Ala Ile Lys His Ala Ala Ser Asn Pro Ser Lys  
    435     440     445  
 Lys Tyr Asn Ile Leu Gly Thr Asn Ala Ile Met Asp Lys Met Arg Val  
    450     455     460  
 Met Gly Leu Arg Arg Gln Arg Asn Tyr Ala Gly Arg Trp Asp Val Leu  
    465     470     475     480  
 Ile Gln Gln Ala Thr Gln Cys Leu Asn Arg Leu Ile Gln Ile Ala Ala  
    485     490     495  
 Arg Lys Lys Arg Asn Tyr Ile Leu Asp Gln Thr Asn Val Tyr Gly Ser  
    500     505     510  
 Ala Gln Arg Arg Lys Met Arg Pro Phe Glu Gly Phe Gln Arg Lys Ala  
    515     520     525  
 Ile Val Ile Cys Pro Thr Asp Glu Asp Leu Lys Asp Arg Thr Ile Lys  
    530     535     540  
 Arg Thr Asp Glu Glu Gly Lys Asp Val Pro Asp His Ala Val Leu Glu  
    545     550     555     560  
 Met Lys Ala Asn Phe Thr Leu Pro Asp Val Gly Asp Phe Leu Asp Glu

Val Leu Phe Ile Glu Leu Gln Arg Glu Glu Ala Asp Lys Leu Val Arg  
580 585 590

Gln Tyr Asn Glu Glu Gly Arg Lys Ala Gly Pro Pro Pro Glu Lys Arg  
595 600 605

Phe Asp Asn Arg Gly Gly Gly Gly Phe Arg Ala Arg Gly Gly Gly Gly  
610 615 620

Ala Phe Gln Arg Tyr Glu Asn Arg Gly Pro Pro Gly Gly Asn Arg Gly  
625 630 635 640

Gly Phe Gln Asn Arg Gly Gly Gly Ser Gly Gly Gly Gly Asn Tyr Arg  
645 650 655

Gly Gly Phe Asn Arg Asn Gly Gly Gly Gly Tyr Ser Gln Asn Arg Trp  
660 665 670

Gly Asn Asn Asn Arg Asp Asn Asn Asn Ser Asn Asn Arg Gly Ser Tyr  
675 680 685

Asn Arg Ala Pro Gln Gln Gln Pro Pro Pro Gln Gln Pro Pro Pro Pro  
690 695 700

Gln Pro Pro Pro Gln Gln Pro Pro Pro Pro Pro Ser Tyr Ser Pro Ala  
705 710 715 720

Arg Asn Pro Pro Gly Ala Ser Thr Tyr Asn Lys Asn Ser Asn Ile Pro  
725 730 735

Gly Ser Ser Ala Asn Thr Ser Thr Pro Thr Val Ser Ser Tyr Ser Pro  
740 745 750

Pro Gln Pro Ser Tyr Ser Gln Pro Pro Tyr Asn Gln Gly Gly Tyr Ser  
755 760 765

Gln Gly Tyr Thr Gly Pro Pro Pro Pro Pro Pro Pro Pro Ala Tyr  
770 775 780

Asn Tyr Gly Ser Tyr Gly Gly Tyr Asn Pro Ala Pro Tyr Thr Pro Pro  
785 790 795 800

Pro Pro Pro Thr Ala Gln Thr Tyr Pro Gln Pro Ser Tyr Asn Gln Tyr  
805 810 815

Gln Gln Tyr Ala Gln Gln Trp Asn Gln Tyr Tyr Gln Asn Gln Gly Gln

820

825

830

Trp Pro Pro Tyr Tyr Gly Asn Tyr Asp Tyr Gly Ser Tyr Ser Gly Asn  
           835                                  840                                  845

Thr Gln Gly Gly Thr Ser Thr Gln  
       850                                  855

<210> 155  
 <211> 232  
 <212> PRT  
 <213> Homo sapiens

<400> 155

Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu  
   1                  5                  10                                  15

Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly  
           20                  25                                  30

Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln  
           35                  40                                  45

Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu  
   50                  55                  60

Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu  
   65                  70                  75                                  80

Met Arg Cys Gly Gly Cys Cys Asn Asp Glu Gly Leu Glu Cys Val Pro  
           85                  90                                  95

Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His  
   100                  105                                  110

Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys  
   115                  120                                  125

Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Lys Lys Ser Val  
   130                  135                                  140

Arg Gly Lys Gly Lys Gly Gln Lys Arg Lys Arg Lys Lys Ser Arg Tyr  
   145                  150                  155                                  160

Lys Ser Trp Ser Val Tyr Val Gly Ala Arg Cys Cys Leu Met Pro Trp  
           165                  170                                  175

Ser Leu Pro Gly Pro His Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys  
           180                  185                                  190



His Leu phe Val Gln Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn  
 195 200 205

Thr Asp Ser Arg Cys Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr  
 210 215 220

Cys Arg Cys Asp Lys Pro Arg Arg  
 225 230

<210> 156  
 <211> 654  
 <212> PRT  
 <213> Homo sapiens

<400> 156

Met Asn Gln Pro Gln Arg Met Ala Pro Val Gly Thr Asp Lys Glu Leu  
 1 5 10 15

Ser Asp Leu Leu Asp Phe Ser Met Met Phe Pro Leu Pro Val Thr Asn  
 20 25 30

Gly Lys Gly Arg Pro Ala Ser Leu Ala Gly Ala Gln Phe Gly Gly Ser  
 35 40 45

Gly Leu Glu Asp Arg Pro Ser Ser Gly Ser Trp Gly Ser Gly Asp Gln  
 50 55 60

Ser Ser Ser Ser Phe Asp Pro Ser Arg Thr Phe Ser Glu Gly Thr His  
 65 70 75 80

Phe Thr Glu Ser His Ser Ser Leu Ser Ser Ser Thr Phe Leu Gly Pro  
 85 90 95

Gly Leu Gly Gly Lys Ser Gly Glu Arg Gly Ala Tyr Ala Ser Phe Gly  
 100 105 110

Arg Asp Ala Gly Val Gly Gly Leu Thr Gln Ala Gly Phe Leu Ser Gly  
 115 120 125

Glu Leu Ala Leu Asn Ser Pro Gly Pro Leu Ser Pro Ser Gly Met Lys  
 130 135 140

Gly Thr Ser Gln Tyr Tyr Pro Ser Tyr Ser Gly Ser Ser Arg Arg Arg  
 145 150 155 160

Ala Ala Asp Gly Ser Leu Asp Thr Gln Pro Lys Lys Val Arg Lys Val  
 165 170 175

Pro Pro Gly Leu Pro Ser Ser Val Tyr Pro Pro Ser Ser Gly Glu Asp  
 180 185 190  
 Tyr Gly Arg Asp Ala Thr Ala Tyr Pro Ser Ala Lys Thr Pro Ser Ser  
 195 200 205  
 Thr Tyr Pro Ala Pro Phe Tyr Val Ala Asp Gly Ser Leu His Pro Ser  
 210 215 220  
 Ala Glu Leu Trp Ser Pro Pro Gly Gln Ala Gly Phe Gly Pro Met Leu  
 225 230 235 240  
 Gly Gly Gly Ser Ser Pro Leu Pro Leu Pro Pro Gly Ser Gly Pro Val  
 245 250 255  
 Gly Ser Ser Gly Ser Ser Ser Thr Phe Gly Gly Leu His Gln His Glu  
 260 265 270  
 Arg Met Gly Tyr Gln Leu His Gly Ala Glu Val Asn Gly Gly Leu Pro  
 275 280 285  
 Ser Ala Ser Ser Phe Ser Ser Ala Pro Gly Ala Thr Tyr Gly Gly Val  
 290 295 300  
 Ser Ser His Thr Pro Pro Val Ser Gly Ala Asp Ser Leu Leu Gly Ser  
 305 310 315 320  
 Arg Gly Thr Thr Ala Gly Ser Ser Gly Asp Ala Leu Gly Lys Ala Leu  
 325 330 335  
 Ala Ser Ile Tyr Ser Pro Asp His Ser Ser Asn Asn Phe Ser Ser Ser  
 340 345 350  
 Pro Ser Thr Pro Val Gly Ser Pro Gln Gly Leu Ala Gly Thr Ser Gln  
 355 360 365  
 Trp Pro Arg Ala Gly Ala Pro Gly Ala Leu Ser Pro Ser Tyr Asp Gly  
 370 375 380  
 Gly Leu His Gly Leu Gln Ser Lys Ile Glu Asp His Leu Asp Glu Ala  
 385 390 395 400  
 Ile His Val Leu Arg Ser His Ala Val Gly Thr Ala Gly Asp Met His  
 405 410 415  
 Thr Leu Leu Pro Gly His Gly Ala Leu Ala Ser Gly Phe Thr Gly Pro  
 420 425 430

Met Ser Leu Gly Gly Arg His Ala Gly Leu Val Gly Gly Ser His Pro  
 435 440 445

Glu Asp Gly Leu Ala Gly Ser Thr Ser Leu Met His Asn His Ala Ala  
 450 455 460

Leu Pro Ser Gln Pro Gly Thr Leu Pro Asp Leu Ser Arg Pro Pro Asp  
 465 470 475 480

Ser Tyr Ser Gly Leu Gly Arg Ala Gly Ala Thr Ala Ala Ala Ser Glu  
 485 490 495

Ile Lys Arg Glu Glu Lys Glu Asp Glu Glu Asn Thr Ser Ala Ala Asp  
 500 505 510

His Ser Glu Glu Glu Lys Lys Glu Leu Lys Ala Pro Arg Ala Arg Thr  
 515 520 525

Ser Pro Asp Glu Asp Glu Asp Asp Leu Leu Pro Pro Glu Gln Lys Ala  
 530 535 540

Glu Arg Glu Lys Glu Arg Arg Val Ala Asn Asn Ala Arg Glu Arg Leu  
 545 550 555 560

Arg Val Arg Asp Ile Asn Glu Ala Phe Lys Glu Leu Gly Arg Met Cys  
 565 570 575

Gln Leu His Leu Asn Ser Glu Lys Pro Gln Thr Lys Leu Leu Ile Leu  
 580 585 590

His Gln Ala Val Ser Val Ile Leu Asn Leu Glu Gln Gln Val Arg Glu  
 595 600 605

Arg Asn Leu Asn Pro Lys Ala Ala Cys Leu Lys Arg Arg Glu Glu Glu  
 610 615 620

Lys Val Ser Gly Val Val Gly Asp Pro Gln Met Val Leu Ser Ala Pro  
 625 630 635 640

His Pro Gly Leu Ser Glu Ala His Asn Pro Ala Gly His Met  
 645 650

<210> 157  
 <211> 284  
 <212> PRT  
 <213> Homo sapiens  
 <400> 157

Met Phe Asp Lys Thr Arg Leu Pro Tyr Val Ala Leu Asp Val Leu Cys  
 1 5 10 15  
 Val Leu Leu Ala Gly Leu Pro Phe Ala Ile Leu Thr Ser Arg His Thr  
 20 25 30  
 Pro Phe Gln Arg Gly Val Phe Cys Asn Asp Glu Ser Ile Lys Tyr Pro  
 35 40 45  
 Tyr Lys Glu Asp Thr Ile Pro Tyr Ala Leu Leu Gly Gly Ile Ile Ile  
 50 55 60  
 Pro Phe Ser Ile Ile Val Ile Ile Leu Gly Glu Thr Leu Ser Val Tyr  
 65 70 75 80  
 Cys Asn Leu Leu His Ser Asn Ser Phe Ile Arg Asn Asn Tyr Ile Ala  
 85 90 95  
 Thr Ile Tyr Lys Ala Ile Gly Thr Phe Leu Phe Gly Ala Ala Ala Ser  
 100 105 110  
 Gln Ser Leu Thr Asp Ile Ala Lys Tyr Ser Ile Gly Arg Leu Arg Pro  
 115 120 125  
 His Phe Leu Asp Val Cys Asp Pro Asp Trp Ser Lys Ile Asn Cys Ser  
 130 135 140  
 Asp Gly Tyr Ile Glu Tyr Tyr Ile Cys Arg Gly Asn Ala Glu Arg Val  
 145 150 155 160  
 Lys Glu Gly Arg Leu Ser Phe Tyr Ser Gly His Ser Ser Phe Ser Met  
 165 170 175  
 Tyr Cys Met Leu Phe Val Ala Leu Tyr Leu Gln Ala Arg Met Lys Gly  
 180 185 190  
 Asp Trp Ala Arg Leu Leu Arg Pro Thr Leu Gln Phe Gly Leu Val Ala  
 195 200 205  
 Val Ser Ile Tyr Val Gly Leu Ser Arg Val Ser Asp Tyr Lys His His  
 210 215 220  
 Trp Ser Asp Val Leu Thr Gly Leu Ile Gln Gly Ala Leu Val Ala Ile  
 225 230 235 240  
 Leu Val Ala Val Tyr Val Ser Asp Phe Phe Lys Glu Arg Thr Ser Phe  
 245 250 255

Lys Glu Arg Lys Glu Glu Asp Ser His Thr Thr Leu His Glu Thr Pro  
 260 265 270

Thr Thr Gly Asn His Tyr Pro Ser Asn His Gln Pro  
 275 280

<210> 158  
 <211> 873  
 <212> PRT  
 <213> Homo sapiens

<400> 158

Met Gln Asp Ala Glu Asn Val Ala Val Pro Glu Ala Ala Glu Glu Arg  
 1 5 10 15

Ala Glu Pro Gly Gln Gln Gln Pro Ala Ala Glu Pro Pro Pro Ala Glu  
 20 25 30

Gly Leu Leu Arg Pro Ala Gly Pro Gly Ala Pro Glu Ala Ala Gly Thr  
 35 40 45

Glu Ala Ser Ser Glu Glu Val Gly Ile Ala Glu Ala Gly Pro Glu Pro  
 50 55 60

Glu Val Arg Thr Glu Pro Ala Ala Glu Ala Glu Ala Ala Ser Gly Pro  
 65 70 75 80

Ser Glu Ser Pro Ser Pro Pro Ala Ala Glu Glu Leu Pro Gly Ser His  
 85 90 95

Ala Glu Pro Pro Val Pro Ala Gln Gly Glu Ala Pro Gly Glu Gln Ala  
 100 105 110

Arg Asp Ala Gly Ser Asp Ser Arg Ala Gln Ala Val Ser Glu Asp Ala  
 115 120 125

Gly Gly Asn Glu Gly Arg Ala Ala Glu Ala Glu Pro Arg Ala Leu Glu  
 130 135 140

Asn Gly Asp Ala Asp Glu Pro Ser Phe Ser Asp Pro Glu Asp Phe Val  
 145 150 155 160

Asp Asp Val Ser Glu Glu Glu Leu Leu Gly Asp Val Leu Lys Asp Arg  
 165 170 175

Pro Gln Glu Ala Asp Gly Ile Asp Ser Val Ile Val Val Asp Asn Val  
 180 185 190

Pro Gln Val Gly Pro Asp Arg Leu Glu Lys Leu Ile Asn Val Ile His

195                      200                      205  
 Lys Ile Phe Ser Lys Phe Gly Lys Ile Thr Asn Asp Phe Tyr Pro Glu  
     210                      215                      220  
 Glu Asp Gly Lys Thr Lys Gly Tyr Ile Phe Leu Glu Tyr Ala Ser Pro  
     225                      230                      235                      240  
 Ala His Ala Val Asp Ala Val Lys Asn Ala Asp Gly Tyr Lys Leu Asp  
                     245                      250                      255  
 Lys Gln His Thr Phe Arg Val Asn Leu Phe Thr Asp Phe Asp Lys Tyr  
                     260                      265                      270  
 Met Thr Ile Ser Asp Glu Trp Asp Ile Pro Glu Lys Gln Pro Phe Lys  
                     275                      280                      285  
 Asp Leu Gly Asn Leu Arg Tyr Trp Leu Glu Glu Ala Glu Cys Arg Asp  
     290                      295                      300  
 Gln Tyr Ser Val Ile Phe Glu Ser Gly Asp Arg Thr Ser Ile Phe Trp  
     305                      310                      315                      320  
 Asn Asp Val Lys Asp Pro Val Ser Ile Glu Glu Arg Ala Arg Trp Thr  
                     325                      330                      335  
 Glu Thr Tyr Val Arg Trp Ser Pro Lys Gly Thr Tyr Leu Ala Thr Phe  
                     340                      345                      350  
 His Gln Arg Gly Ile Ala Leu Trp Gly Gly Glu Lys Phe Lys Gln Ile  
                     355                      360                      365  
 Gln Arg Phe Ser His Gln Gly Val Gln Leu Ile Asp Phe Ser Pro Cys  
     370                      375                      380  
 Glu Arg Tyr Leu Val Thr Phe Ser Pro Leu Met Asp Thr Gln Asp Asp  
     385                      390                      395                      400  
 Pro Gln Ala Ile Ile Ile Trp Asp Ile Leu Thr Gly His Lys Lys Arg  
                     405                      410                      415  
 Gly Phe His Cys Glu Ser Ser Ala His Trp Pro Ile Phe Lys Trp Ser  
                     420                      425                      430  
 His Asp Gly Lys Phe Phe Ala Arg Met Thr Leu Asp Thr Leu Ser Ile  
                     435                      440                      445  
 Tyr Glu Thr Pro Ser Met Gly Leu Leu Asn Lys Lys Ser Leu Lys Ile

450                      455                      460  
 Ser Gly Ile Lys Asp Phe Ser Trp Ser Pro Gly Gly Asn Ile Ile Ala  
 465                      470                      475                      480  
 Phe Trp Val Pro Glu Asp Lys Asp Ile Pro Ala Arg Val Thr Leu Met  
                     485                      490                      495  
 Gln Leu Pro Thr Arg Gln Glu Ile Arg Val Arg Asn Leu Phe Asn Val  
                     500                      505                      510  
 Val Asp Cys Lys Leu His Trp Gln Lys Asn Gly Asp Tyr Leu Cys Val  
                     515                      520                      525  
 Lys Val Asp Arg Thr Pro Lys Gly Thr Gln Gly Val Val Thr Asn Phe  
                     530                      535                      540  
 Glu Ile Phe Arg Met Arg Glu Lys Gln Val Pro Val Asp Val Val Glu  
 545                      550                      555                      560  
 Met Lys Glu Thr Ile Ile Ala Phe Ala Trp Glu Pro Asn Gly Ser Lys  
                     565                      570                      575  
 Phe Ala Val Leu His Gly Glu Ala Pro Arg Ile Ser Val Ser Phe Tyr  
                     580                      585                      590  
 His Val Lys Asn Asn Gly Lys Ile Glu Leu Ile Lys Met Phe Asp Lys  
                     595                      600                      605  
 Gln Gln Ala Asn Thr Ile Phe Trp Ser Pro Gln Gly Gln Phe Val Val  
                     610                      615                      620  
 Leu Ala Gly Leu Arg Ser Met Asn Gly Ala Leu Ala Phe Val Asp Thr  
 625                      630                      635                      640  
 Ser Asp Cys Thr Val Met Asn Ile Ala Glu His Tyr Met Ala Ser Asp  
                     645                      650                      655  
 Val Glu Trp Asp Pro Thr Gly Arg Tyr Val Val Thr Ser Val Ser Trp  
                     660                      665                      670  
 Trp Ser His Lys Val Asp Asn Ala Tyr Trp Leu Trp Thr Phe Gln Gly  
                     675                      680                      685  
 Arg Leu Leu Gln Lys Asn Asn Lys Asp Arg Phe Cys Gln Leu Leu Trp  
                     690                      695                      700  
 Ara Pro Ara Pro Pro Thr Leu Leu Ser Gl                      Ile Lys Gln Ile

705                      710                      715                      720  
 Lys Lys Asp Leu Lys Lys Tyr Ser Lys Ile Phe Glu Gln Lys Asp Arg  
                                  725                                   730                                   735  
 Leu Ser Gln Ser Lys Ala Ser Lys Glu Leu Val Glu Arg Arg Arg Thr  
                                  740                                   745                                   750  
 Met Met Glu Asp Phe Arg Lys Tyr Arg Lys Met Ala Gln Glu Leu Tyr  
                                  755                                   760                                   765  
 Met Glu Gln Lys Asn Glu Arg Leu Glu Leu Arg Gly Gly Val Asp Thr  
                                  770                                   775                                   780  
 Asp Glu Leu Asp Ser Asn Val Asp Asp Trp Glu Glu Glu Thr Ile Glu  
                                  785                                   790                                   795                                   800  
 Phe Phe Val Thr Glu Glu Ile Ile Pro Leu Gly Ile Arg Ser Asp Leu  
                                  805                                   810                                   815  
 Glu His Cys Ala Gln Pro Cys Val Leu Trp Ser Arg Gly Arg Pro Ala  
                                  820                                   825                                   830  
 Gly Ser Arg Val Thr Pro Ala Ser Ser Leu Cys Ser Leu Ala Leu Asp  
                                  835                                   840                                   845  
 Cys Asp Cys Ala Trp Ile Leu Pro Leu Arg His Ile Phe Val Pro Phe  
                                  850                                   855                                   860  
 Ser Pro Trp Cys Leu Gln Trp Gly Ile  
                                  865                                   870  
  
 <210> 159  
 <211> 90  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 159  
 Ala Ala Asn Ala Thr Thr Asn Pro Ser Gln Leu Leu Pro Leu Glu Leu  
 1                                   5                                   10                                   15  
 Val Asp Lys Cys Ile Gly Ser Arg Ile His Ile Val Met Lys Ser Asp  
                                  20                                   25                                   30  
 Lys Glu Ile Val Gly Thr Leu Leu Gly Phe Asp Asp Phe Val Asn Met  
                                  35                                   40                                   45  
 Val Leu Glu Asp Val Thr Glu Phe Glu Ile Thr Pro Glu Gly Arg Arg  
                                  50                                   55                                   60



Ile Thr Lys Leu Asp Gln Ile Leu Leu Asn Gly Asn Asn Ile Thr Met  
65 70 75 80

Leu Val Pro Gly Gly Glu Gly Pro Glu Val  
85 90

<210> 160  
<211> 864  
<212> PRT  
<213> Homo sapiens

<400> 160

Gln Val Gln His Gly Ser Asn Val Asn Ile His Arg Leu Val Glu Gly  
1 5 10 15

Asn Val Val Ile Trp Glu Asn Ala Ser Thr Pro Leu Tyr Thr Gly Ala  
20 25 30

Ile Val Thr Asn Asn Asp Gly Pro Tyr Met Ala Tyr Val Glu Val Leu  
35 40 45

Gly Asp Pro Asn Leu Gln Phe Phe Ile Lys Ser Gly Asp Ala Trp Val  
50 55 60

Thr Leu Ser Glu His Glu Tyr Leu Ala Lys Leu Gln Glu Ile Arg Gln  
65 70 75 80

Ala Val His Ile Glu Ser Val Phe Ser Leu Asn Met Ala Phe Gln Leu  
85 90 95

Glu Asn Asn Lys Tyr Glu Val Glu Thr His Ala Lys Asn Gly Ala Asn  
100 105 110

Met Val Thr Phe Ile Pro Arg Asn Gly His Ile Cys Lys Met Val Tyr  
115 120 125

His Lys Asn Val Arg Ile Tyr Lys Ala Thr Gly Asn Asp Thr Val Thr  
130 135 140

Ser Val Val Gly Phe Phe Arg Gly Leu Arg Leu Leu Leu Ile Asn Val  
145 150 155 160

Phe Ser Ile Asp Asp Asn Gly Met Met Ser Asn Arg Tyr Phe Gln His  
165 170 175

Val Asp Asp Lys Tyr Val Pro Ile Ser Gln Lys Asn Tyr Glu Thr Gly  
180 185 190

Ile Val Lys Leu Lys Asp Tyr Lys His Ala Tyr His Pro Val Asp Leu  
 195 200 205  
 Asp Ile Lys Asp Ile Asp Tyr Thr Met Phe His Leu Ala Asp Ala Thr  
 210 215 220  
 Tyr His Glu Pro Cys Phe Lys Ile Ile Pro Asn Thr Gly Phe Cys Ile  
 225 230 235 240  
 Thr Lys Leu Phe Asp Gly Asp Gln Val Leu Tyr Glu Ser Phe Asn Pro  
 245 250 255  
 Leu Ile His Cys Ile Asn Glu Val His Ile Tyr Asp Arg Asn Asn Gly  
 260 265 270  
 Ser Ile Ile Cys Leu His Leu Asn Tyr Ser Pro Pro Ser Tyr Lys Ala  
 275 280 285  
 Tyr Leu Val Leu Lys Asp Thr Gly Trp Glu Ala Thr Thr His Pro Leu  
 290 295 300  
 Leu Glu Glu Lys Ile Glu Glu Leu Gln Asp Gln Arg Ala Cys Glu Leu  
 305 310 315 320  
 Asp Val Asn Phe Ile Ser Asp Lys Asp Leu Tyr Val Ala Ala Leu Thr  
 325 330 335  
 Asn Ala Asp Leu Asn Tyr Thr Met Val Thr Pro Arg Pro His Arg Asp  
 340 345 350  
 Val Ile Arg Val Ser Asp Gly Ser Glu Val Leu Trp Tyr Tyr Glu Gly  
 355 360 365  
 Leu Asp Asn Phe Leu Val Cys Ala Trp Ile Tyr Val Ser Asp Gly Val  
 370 375 380  
 Ala Ser Leu Val His Leu Arg Ile Lys Asp Arg Ile Pro Ala Asn Asn  
 385 390 395 400  
 Asp Ile Tyr Val Leu Lys Gly Asp Leu Tyr Trp Thr Arg Ile Thr Lys  
 405 410 415  
 Ile Gln Phe Thr Gln Glu Ile Lys Arg Leu Val Lys Lys Ser Lys Lys  
 420 425 430  
 Lys Leu Ala Pro Ile Thr Glu Glu Asp Ser Asp Lys His Asp Glu Pro  
 435 440 445

Pro Glu Gly Pro Gly Ala Ser Gly Leu Pro Pro Lys Ala Pro Gly Asp  
 450 455 460  
 Lys Glu Gly Ser Glu Gly His Lys Gly Pro Ser Lys Gly Ser Asp Ser  
 465 470 475 480  
 Ser Lys Glu Gly Lys Lys Pro Gly Ser Gly Lys Lys Pro Gly Pro Ala  
 485 490 495  
 Arg Glu His Lys Pro Ser Lys Ile Pro Thr Leu Ser Lys Lys Pro Ser  
 500 505 510  
 Gly Pro Lys Asp Pro Lys His Pro Arg Asp Pro Lys Glu Pro Arg Lys  
 515 520 525  
 Ser Lys Ser Pro Arg Thr Ala Ser Pro Thr Arg Arg Pro Ser Pro Lys  
 530 535 540  
 Leu Pro Gln Leu Ser Lys Leu Pro Lys Ser Thr Ser Pro Arg Ser Pro  
 545 550 555 560  
 Pro Pro Pro Thr Arg Pro Ser Ser Pro Glu Arg Pro Glu Gly Thr Lys  
 565 570 575  
 Ile Ile Lys Thr Ser Lys Pro Pro Ser Pro Lys Pro Pro Phe Asp Pro  
 580 585 590  
 Ser Phe Lys Glu Lys Phe Tyr Asp Asp Tyr Ser Lys Ala Ala Ser Arg  
 595 600 605  
 Ser Lys Glu Thr Lys Thr Thr Val Val Leu Asp Glu Ser Phe Glu Ser  
 610 615 620  
 Ile Leu Lys Glu Thr Leu Pro Glu Thr Pro Gly Thr Pro Phe Thr Thr  
 625 630 635 640  
 Pro Arg Pro Val Pro Pro Lys Arg Pro Arg Thr Pro Glu Ser Pro Phe  
 645 650 655  
 Glu Pro Pro Lys Asp Pro Asp Ser Pro Ser Thr Ser Pro Ser Glu Phe  
 660 665 670  
 Phe Thr Pro Pro Glu Ser Lys Arg Thr Arg Phe His Glu Thr Pro Ala  
 675 680 685  
 Asp Thr Pro Leu Pro Asp Val Thr Ala Glu Leu Phe Lys Glu Pro Asp  
 690 695 700

Val Thr Ala Glu Thr Lys Ser Pro Asp Glu Ala Met Lys Arg Pro Arg  
705 710 715 720

Ser Pro Ser Glu Tyr Glu Asp Thr Ser Pro Gly Asp Tyr Pro Ser Leu  
725 730 735

Pro Met Lys Arg His Arg Leu Glu Arg Leu Arg Leu Thr Thr Thr Glu  
740 745 750

Met Glu Thr Asp Pro Gly Arg Met Ala Lys Asp Ala Ser Gly Lys Pro  
755 760 765

Val Lys Leu Lys Arg Ser Lys Ser Phe Asp Asp Leu Thr Thr Val Glu  
770 775 780

Leu Ala Pro Glu Pro Lys Ala Ser Arg Ile Val Val Asp Asp Glu Gly  
785 790 795 800

Thr Glu Ala Asp Asp Glu Glu Thr His Pro Pro Glu Glu Arg Gln Lys  
805 810 815

Thr Glu Val Arg Arg Arg Arg Pro Pro Lys Lys Pro Ser Lys Ser Pro  
820 825 830

Arg Pro Ser Lys Pro Lys Lys Pro Lys Lys Pro Asp Ser Ala Tyr Ile  
835 840 845

Pro Ser Ile Leu Ala Ile Leu Val Val Ser Leu Ile Val Gly Ile Leu  
850 855 860

<210> 161  
<211> 269  
<212> PRT  
<213> Homo sapiens

<400> 161

Met Tyr Arg Asn Pro Gly Pro Ser Gly Pro Gln Leu Arg Asp Phe Ser  
1 5 10 15

Ser Ile Ile Gln Thr Cys Ser Gly Asn Ile Gln Arg Ile Ser Gln Ala  
20 25 30

Thr Ala Gln Ile Lys Asn Leu Met Ser Gln Leu Gly Thr Lys Gln Asp  
35 40 45

Ser Ser Lys Leu Gln Glu Asn Leu Gln Gln Leu Gln His Ser Thr Asn  
50 55 60

Gln Leu Ala Lys Glu Thr Asn Glu Leu Leu Lys Glu Leu Gly Ser Leu  
65 70 75 80

Pro Leu Pro Leu Ser Thr Ser Glu Gln Arg Gln Gln Arg Leu Gln Lys  
85 90 95

Glu Arg Leu Met Asn Asp Phe Ser Ala Ala Leu Asn Asn Phe Gln Ala  
100 105 110

Val Gln Arg Arg Val Ser Glu Lys Glu Lys Glu Ser Ile Ala Arg Ala  
115 120 125

Arg Ala Gly Ser Arg Leu Ser Ala Glu Glu Arg Gln Arg Glu Glu Gln  
130 135 140

Leu Val Ser Phe Asp Ser His Glu Glu Trp Asn Gln Met Gln Ser Gln  
145 150 155 160

Glu Asp Glu Val Ala Ile Thr Glu Gln Asp Leu Glu Leu Ile Lys Glu  
165 170 175

Arg Glu Thr Ala Ile Arg Gln Leu Glu Ala Asp Ile Leu Asp Val Asn  
180 185 190

Gln Ile Phe Lys Asp Leu Ala Met Met Ile His Asp Gln Gly Asp Leu  
195 200 205

Ile Asp Ser Ile Glu Ala Asn Val Glu Ser Ser Glu Val His Val Glu  
210 215 220

Arg Ala Thr Glu Gln Leu Gln Arg Ala Ala Tyr Tyr Gln Lys Lys Ser  
225 230 235 240

Arg Lys Lys Met Cys Ile Leu Val Leu Val Leu Ser Val Ile Ile Leu  
245 250 255

Ile Leu Gly Leu Ile Ile Trp Leu Val Tyr Lys Thr Lys  
260 265

<210> 162  
<211> 513  
<212> PRT  
<213> Homo sapiens

<400> 162

Met Ala Ser Gly Ser Val Ala Glu Cys Leu Gln Gln Glu Thr Thr Cys  
1 5 10 15

Pro Val Cys Leu Gln Tyr Phe Ala Glu P Leu Asp Cys Glv

20 25 30  
 His Asn Ile Cys Cys Ala Cys Leu Ala Arg Cys Trp Gly Thr Ala Glu  
 35 40 45  
 Thr Asn Val Ser Cys Pro Gln Cys Arg Glu Thr Phe Pro Gln Arg His  
 50 55 60  
 Met Arg Pro Asn Arg His Leu Ala Asn Val Thr Gln Leu Val Lys Gln  
 65 70 75 80  
 Leu Arg Thr Glu Arg Pro Ser Gly Pro Gly Gly Glu Met Gly Val Cys  
 85 90 95  
 Glu Lys His Arg Glu Pro Leu Lys Leu Tyr Cys Glu Glu Asp Gln Met  
 100 105 110  
 Pro Ile Cys Val Val Cys Asp Arg Ser Arg Glu His Arg Gly His Ser  
 115 120 125  
 Val Leu Pro Leu Glu Glu Ala Val Glu Gly Phe Lys Glu Gln Ile Gln  
 130 135 140  
 Asn Gln Leu Asp His Leu Lys Arg Val Lys Asp Leu Lys Lys Arg Arg  
 145 150 155 160  
 Arg Ala Gln Gly Glu Gln Ala Arg Ala Glu Leu Leu Ser Leu Thr Gln  
 165 170 175  
 Met Glu Arg Glu Lys Ile Val Trp Glu Phe Glu Gln Leu Tyr His Ser  
 180 185 190  
 Leu Lys Glu His Glu Tyr Arg Leu Leu Ala Arg Leu Glu Glu Leu Asp  
 195 200 205  
 Leu Ala Ile Tyr Asn Ser Ile Asn Gly Ala Ile Thr Gln Phe Ser Cys  
 210 215 220  
 Asn Ile Ser His Leu Ser Ser Leu Ile Ala Gln Leu Glu Glu Lys Gln  
 225 230 235 240  
 Gln Gln Pro Thr Arg Glu Leu Leu Gln Asp Ile Gly Asp Thr Leu Ser  
 245 250 255  
 Arg Ala Glu Arg Ile Arg Ile Pro Glu Pro Trp Ile Thr Pro Pro Asp  
 260 265 270  
 Leu Gln Glu Lys Ile His Ile Phe Ala Gln Lys Cys Leu Phe Leu Thr

275                      280                      285  
 Glu Ser Leu Lys Gln Phe Thr Glu Lys Met Gln Ser Asp Met Glu Lys  
     290                      295                      300  
 Ile Gln Glu Leu Arg Glu Ala Gln Leu Tyr Ser Val Asp Val Thr Leu  
     305                      310                      315                      320  
 Asp Pro Asp Thr Ala Tyr Pro Ser Leu Ile Leu Ser Asp Asn Leu Arg  
                     325                      330                      335  
 Gln Val Arg Tyr Ser Tyr Leu Gln Gln Asp Leu Pro Asp Asn Pro Glu  
                     340                      345                      350  
 Arg Phe Asn Leu Phe Pro Cys Val Leu Gly Ser Pro Cys Phe Ile Ala  
                     355                      360                      365  
 Gly Arg His Tyr Trp Glu Val Glu Val Gly Asp Lys Ala Lys Trp Thr  
                     370                      375                      380  
 Ile Gly Val Cys Glu Asp Ser Val Cys Arg Lys Gly Gly Val Thr Ser  
     385                      390                      395                      400  
 Ala Pro Gln Asn Gly Phe Trp Ala Val Ser Leu Trp Tyr Gly Lys Glu  
                     405                      410                      415  
 Tyr Trp Ala Leu Thr Ser Pro Met Thr Ala Leu Pro Leu Arg Thr Pro  
                     420                      425                      430  
 Leu Gln Arg Val Gly Ile Phe Leu Asp Tyr Asp Ala Gly Glu Val Ser  
                     435                      440                      445  
 Phe Tyr Asn Val Thr Glu Arg Cys His Thr Phe Thr Phe Ser His Ala  
                     450                      455                      460  
 Thr Phe Cys Gly Pro Val Arg Pro Tyr Phe Ser Leu Ser Tyr Ser Gly  
     465                      470                      475                      480  
 Gly Lys Ser Ala Ala Pro Leu Ile Ile Cys Pro Met Ser Gly Ile Asp  
                     485                      490                      495  
 Gly Phe Ser Gly His Val Gly Asn His Gly His Ser Met Glu Thr Ser  
                     500                      505                      510

Pro

&lt;210&gt; 163

<211> 1010  
 <212> PRT  
 <213> Homo sapiens

<400> 163

Met Ala Ala Arg Val Leu Ile Ile Gly Ser Gly Gly Arg Glu His Thr  
 1 5 10 15

Leu Ala Trp Lys Leu Ala Gln Ser His His Val Lys Gln Val Leu Val  
 20 25 30

Ala Pro Gly Asn Ala Gly Thr Ala Cys Ser Glu Lys Ile Ser Asn Thr  
 35 40 45

Ala Ile Ser Ile Ser Asp His Thr Ala Leu Ala Gln Phe Cys Lys Glu  
 50 55 60

Lys Lys Ile Glu Phe Val Val Val Gly Pro Glu Ala Pro Leu Ala Ala  
 65 70 75 80

Gly Ile Val Gly Asn Leu Arg Ser Ala Gly Val Gln Cys Phe Gly Pro  
 85 90 95

Thr Ala Glu Ala Ala Gln Leu Glu Ser Ser Lys Arg Phe Ala Lys Glu  
 100 105 110

Phe Met Asp Arg His Gly Ile Pro Thr Ala Gln Trp Lys Ala Phe Thr  
 115 120 125

Lys Pro Glu Glu Ala Cys Ser Phe Ile Leu Ser Ala Asp Phe Pro Ala  
 130 135 140

Leu Val Val Lys Ala Ser Gly Leu Ala Ala Gly Lys Gly Val Ile Val  
 145 150 155 160

Ala Lys Ser Lys Glu Glu Ala Cys Lys Ala Val Gln Glu Ile Met Gln  
 165 170 175

Glu Lys Ala Phe Gly Ala Ala Gly Glu Thr Ile Val Ile Glu Glu Leu  
 180 185 190

Leu Asp Gly Glu Glu Val Ser Cys Leu Cys Phe Thr Asp Gly Lys Thr  
 195 200 205

Val Ala Pro Met Pro Pro Ala Gln Asp His Lys Arg Leu Leu Glu Gly  
 210 215 220

Asp Gly Gly Pro Asn Thr Gly Gly Met Gly Ala Tyr Cys Pro Ala Pro  
 225 230 240



Gln Val Ser Asn Asp Leu Leu Leu Lys Ile Lys Asp Thr Val Leu Gln  
 245 250 255  
 Arg Thr Val Asp Gly Met Gln Gln Glu Gly Thr Pro Tyr Thr Gly Ile  
 260 265 270  
 Leu Tyr Ala Gly Ile Met Leu Thr Lys Asn Gly Pro Lys Val Leu Glu  
 275 280 285  
 Phe Asn Cys Arg Phe Gly Asp Pro Glu Cys Gln Val Ile Leu Pro Leu  
 290 295 300  
 Leu Lys Ser Asp Leu Tyr Glu Val Ile Gln Ser Thr Leu Asp Gly Leu  
 305 310 315 320  
 Leu Cys Thr Ser Leu Pro Val Trp Leu Glu Asn His Thr Ala Leu Thr  
 325 330 335  
 Val Val Met Ala Ser Lys Gly Tyr Pro Gly Asp Tyr Thr Lys Gly Val  
 340 345 350  
 Glu Ile Thr Gly Phe Pro Glu Ala Gln Ala Leu Gly Leu Glu Val Phe  
 355 360 365  
 His Ala Gly Thr Ala Leu Lys Asn Gly Lys Val Val Thr His Gly Gly  
 370 375 380  
 Arg Val Leu Ala Val Thr Ala Ile Arg Glu Asn Leu Ile Ser Ala Leu  
 385 390 395 400  
 Glu Glu Ala Lys Lys Gly Leu Ala Ala Ile Lys Phe Glu Gly Ala Ile  
 405 410 415  
 Tyr Arg Lys Asp Val Gly Phe Arg Ala Ile Ala Phe Leu Gln Gln Pro  
 420 425 430  
 Arg Ser Leu Thr Tyr Lys Glu Ser Gly Val Asp Ile Ala Ala Gly Asn  
 435 440 445  
 Met Leu Val Lys Lys Ile Gln Pro Leu Ala Lys Ala Thr Ser Arg Ser  
 450 455 460  
 Gly Cys Lys Val Asp Leu Gly Gly Phe Ala Gly Leu Phe Asp Leu Lys  
 465 470 475 480  
 Ala Ala Gly Phe Lys Asp Pro Leu Leu Ala Ser Gly Thr Asp Gly Val  
 485 490 495

Gly Thr Lys Leu Lys Ile Ala Gln Leu Cys Asn Lys His Asp Thr Ile  
 500 505 510

Gly Gln Asp Leu Val Ala Met Cys Val Asn Asp Ile Leu Ala Gln Gly  
 515 520 525

Ala Glu Pro Leu Phe Phe Leu Asp Tyr Phe Ser Cys Gly Lys Leu Asp  
 530 535 540

Leu Ser Val Thr Glu Ala Val Val Ala Gly Ile Ala Lys Ala Cys Gly  
 545 550 555 560

Lys Ala Gly Cys Ala Leu Leu Gly Gly Glu Thr Ala Glu Met Pro Asp  
 565 570 575

Met Tyr Pro Pro Gly Glu Tyr Asp Leu Ala Gly Phe Ala Val Gly Ala  
 580 585 590

Met Glu Arg Asp Gln Lys Leu Pro His Leu Glu Arg Ile Thr Glu Gly  
 595 600 605

Asp Val Val Val Gly Ile Ala Ser Ser Gly Leu His Ser Asn Gly Phe  
 610 615 620

Ser Leu Val Arg Lys Ile Val Ala Lys Ser Ser Leu Gln Tyr Ser Ser  
 625 630 635 640

Pro Ala Pro Asp Gly Cys Gly Asp Gln Thr Leu Gly Asp Leu Leu Leu  
 645 650 655

Thr Pro Thr Arg Ile Tyr Ser His Ser Leu Leu Pro Val Leu Arg Ser  
 660 665 670

Gly His Val Lys Ala Phe Ala His Ile Thr Gly Gly Gly Leu Leu Glu  
 675 680 685

Asn Ile Pro Arg Val Leu Pro Glu Lys Leu Gly Val Asp Leu Asp Ala  
 690 695 700

Gln Thr Trp Arg Ile Pro Arg Val Phe Ser Trp Leu Gln Gln Glu Gly  
 705 710 715 720

His Leu Ser Glu Glu Glu Met Ala Arg Thr Phe Asn Cys Gly Val Gly  
 725 730 735

Ala Val Leu Val Val Ser Lys Glu Gln Thr Glu Gln Ile Leu Arg Asp  
 740 745 750

Ile Gln Gln His Lys Glu Glu Ala Trp Val Ile Gly Ser Val Val Ala  
 755 760 765  
 Arg Ala Glu Gly Ser Pro Arg Val Lys Val Lys Asn Leu Ile Glu Ser  
 770 775 780  
 Met Gln Ile Asn Gly Ser Val Leu Lys Asn Gly Ser Leu Thr Asn His  
 785 790 795 800  
 Phe Ser Phe Glu Lys Lys Lys Ala Arg Val Ala Val Leu Ile Ser Gly  
 805 810 815  
 Thr Gly Ser Asn Leu Gln Ala Leu Ile Asp Ser Thr Arg Glu Pro Asn  
 820 825 830  
 Ser Ser Ala Gln Ile Asp Ile Val Ile Ser Asn Lys Ala Ala Val Ala  
 835 840 845  
 Gly Leu Asp Lys Ala Glu Arg Ala Gly Ile Pro Thr Arg Val Ile Asn  
 850 855 860  
 His Lys Leu Tyr Lys Asn Arg Val Glu Phe Asp Ser Ala Ile Asp Leu  
 865 870 875 880  
 Val Leu Glu Glu Phe Ser Ile Asp Ile Val Cys Leu Ala Gly Phe Met  
 885 890 895  
 Arg Ile Leu Ser Gly Pro Phe Val Gln Lys Trp Asn Gly Lys Met Leu  
 900 905 910  
 Asn Ile His Pro Ser Leu Leu Pro Ser Phe Lys Gly Ser Asn Ala His  
 915 920 925  
 Glu Gln Ala Leu Glu Thr Gly Val Thr Val Thr Gly Cys Thr Val His  
 930 935 940  
 Phe Val Ala Glu Asp Val Asp Ala Gly Gln Ile Ile Leu Gln Glu Ala  
 945 950 955 960  
 Val Pro Val Lys Arg Gly Asp Thr Val Ala Thr Leu Ser Glu Arg Val  
 965 970 975  
 Lys Leu Ala Glu His Lys Ile Phe Pro Ala Ala Leu Gln Leu Val Ala  
 980 985 990  
 Ser Gly Thr Val Gln Leu Gly Glu Asn Gly Lys Ile Cys Trp Val Lys  
 995 1000 1005

Glu Glu  
1010

<210> 164  
<211> 411  
<212> PRT  
<213> Homo sapiens

<400> 164

Glu Ala Gly Pro Ala Pro Leu Ser Ala Ala Ala Pro Gly Ala Gly Arg  
1 5 10 15

Gly Trp Pro Arg Pro Leu Ala Glu Arg Arg Lys Gly Arg Gly Arg Arg  
20 25 30

Gln Pro Leu Arg Ala Arg Leu Asn Arg Arg Arg Trp Ala Ala Gly Gln  
35 40 45

Gly Ser Thr Val Gln Ala Ala Thr Phe Gly Pro Ala Met Ala Ala Ala  
50 55 60

Pro Leu Lys Val Cys Ile Val Gly Ser Gly Asn Trp Gly Ser Ala Val  
65 70 75 80

Ala Lys Ile Ile Gly Asn Asn Val Lys Lys Leu Gln Lys Phe Ala Ser  
85 90 95

Thr Val Lys Met Trp Val Phe Glu Glu Thr Val Asn Gly Arg Lys Leu  
100 105 110

Thr Asp Ile Ile Asn Asn Asp His Glu Asn Val Lys Tyr Leu Pro Gly  
115 120 125

His Lys Leu Pro Glu Asn Val Val Ala Met Ser Asn Leu Ser Glu Ala  
130 135 140

Val Gln Asp Ala Asp Leu Leu Val Phe Val Ile Pro His Gln Phe Ile  
145 150 155 160

His Arg Ile Cys Asp Glu Ile Thr Gly Arg Val Pro Lys Lys Ala Leu  
165 170 175

Gly Ile Thr Leu Ile Lys Gly Ile Asp Glu Gly Pro Glu Gly Leu Lys  
180 185 190

Leu Ile Ser Asp Ile Ile Arg Glu Lys Met Gly Ile Asp Ile Ser Val  
195 200 205

Leu Met Gly Ala Asn Ile Ala Asn Glu Val Ala Ala Glu Lys Phe Cys  
 210 215 220

Glu Thr Thr Ile Gly Ser Lys Val Met Glu Asn Gly Leu Leu Phe Lys  
 225 230 235 240

Glu Leu Leu Gln Thr Pro Asn Phe Arg Ile Thr Val Val Asp Asp Ala  
 245 250 255

Asp Thr Val Glu Leu Cys Gly Ala Leu Lys Asn Ile Val Ala Val Gly  
 260 265 270

Ala Gly Phe Cys Asp Gly Leu Arg Cys Gly Asp Asn Thr Lys Ala Ala  
 275 280 285

Val Ile Arg Leu Gly Leu Met Glu Met Ile Ala Phe Ala Arg Ile Phe  
 290 295 300

Cys Lys Gly Gln Val Ser Thr Ala Thr Phe Leu Glu Ser Cys Gly Val  
 305 310 315 320

Ala Asp Leu Ile Thr Thr Cys Tyr Gly Gly Arg Asn Arg Arg Val Ala  
 325 330 335

Glu Ala Phe Ala Arg Thr Gly Lys Thr Ile Glu Glu Leu Glu Lys Glu  
 340 345 350

Met Leu Asn Gly Gln Lys Leu Gln Gly Pro Gln Thr Ser Ala Glu Val  
 355 360 365

Tyr Arg Ile Leu Lys Gln Lys Gly Leu Leu Asp Lys Phe Pro Leu Phe  
 370 375 380

Thr Ala Val Tyr Gln Ile Cys Tyr Glu Ser Arg Pro Val Gln Glu Met  
 385 390 395 400

Leu Ser Cys Leu Gln Ser His Pro Glu His Thr  
 405 410

<210> 165  
 <211> 890  
 <212> PRT  
 <213> Homo sapiens

<400> 165

His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys Arg Arg Gln Asp Val  
 1 5 10 15

Ser Pro Asn Arg Asp Phe Leu Thr His Phe Tyr Asn Ile Met His Cys  
 20 25 30  
 Gly Leu Leu His Ile Asp Gln Asp Ile Val Asn Thr Ile Ile Lys His  
 35 40 45  
 Cys Ser Pro Gln Phe Phe Ser Leu Gly Leu Pro Gly Ala Thr Met Leu  
 50 55 60  
 Ile Met Asp Phe Ile Val Ala Ala Gly Arg Val Ala Ser Ser Ala Phe  
 65 70 75 80  
 Leu Asn Ala Pro Arg Val Glu Ala Gln Val Leu Leu Gly Ser Leu Val  
 85 90 95  
 Cys Phe Pro Asn Leu Tyr Cys Glu Leu Pro Ser Leu His Pro Asn Ile  
 100 105 110  
 Pro Asp Val Ala Val Ser Gln Phe Thr Asp Val Lys Glu Leu Ile Ile  
 115 120 125  
 Lys Thr Val Leu Ser Ser Ala Arg Asp Glu Pro Ser Gly Pro Ala Arg  
 130 135 140  
 Cys Val Ala Leu Cys Ser Leu Gly Ile Trp Ile Cys Glu Glu Leu Val  
 145 150 155 160  
 His Glu Ser His His Pro Gln Ile Lys Glu Ala Leu Asn Val Ile Cys  
 165 170 175  
 Val Ser Leu Lys Phe Thr Asn Lys Thr Val Ala His Val Ala Cys Asn  
 180 185 190  
 Met Leu His Met Leu Val His Tyr Val Pro Arg Leu Gln Ile Tyr Gln  
 195 200 205  
 Pro Asp Ser Pro Leu Lys Ile Ile Gln Ile Leu Ile Ala Thr Ile Thr  
 210 215 220  
 His Leu Leu Pro Ser Thr Glu Ala Ser Ser Tyr Glu Met Asp Lys Arg  
 225 230 235 240  
 Leu Val Val Ser Leu Leu Leu Cys Leu Leu Asp Trp Ile Met Ala Leu  
 245 250 255  
 Pro Leu Lys Thr Leu Leu Gln Pro Phe His Ala Thr Gly Ala Glu Ser  
 260 265 270

Asp Lys Thr Glu Lys Ser Val Leu Asn Cys Ile Tyr Lys Val Leu His  
275 280 285

Gly Cys Val Tyr Gly Ala Gln Cys Phe Ser Asn Pro Arg Tyr Phe Pro  
290 295 300

Met Ser Leu Ser Asp Leu Ala Ser Val Asp Tyr Asp Pro Phe Met His  
305 310 315 320

Leu Glu Ser Leu Lys Glu Pro Glu Pro Leu His Ser Pro Asp Ser Glu  
325 330 335

Arg Ser Ser Lys Leu Gln Pro Val Thr Glu Val Lys Thr Gln Met Gln  
340 345 350

His Gly Leu Ile Ser Ile Ala Ala Arg Thr Val Ile Thr His Leu Val  
355 360 365

Asn His Leu Gly His Tyr Pro Met Ser Gly Gly Pro Ala Met Leu Thr  
370 375 380

Ser Gln Val Cys Glu Asn His Asp Asn His Tyr Ser Glu Ser Thr Glu  
385 390 395 400

Leu Ser Pro Glu Leu Phe Glu Ser Pro Asn Ile Gln Phe Phe Val Leu  
405 410 415

Asn Asn Thr Thr Leu Val Ser Cys Ile Gln Ile Arg Ser Glu Glu Asn  
420 425 430

Met Pro Gly Gly Gly Leu Ser Ala Gly Leu Ala Ser Ala Asn Ser Asn  
435 440 445

Val Arg Ile Ile Val Arg Asp Leu Ser Gly Lys Tyr Ser Trp Asp Ser  
450 455 460

Ala Ile Leu Tyr Gly Pro Pro Pro Val Ser Gly Leu Ser Glu Pro Thr  
465 470 475 480

Ser Phe Met Leu Ser Leu Ser His Gln Glu Lys Pro Glu Glu Pro Pro  
485 490 495

Thr Ser Asn Glu Cys Leu Glu Asp Ile Thr Val Lys Asp Gly Leu Ser  
500 505 510

Leu Gln Phe Lys Arg Phe Arg Glu Thr Val Pro Thr Trp Asp Thr Ile  
515 520 525

Arg Asp Glu Val Asp Val Leu Asp Glu Leu Leu Glu Tyr Leu Gly Val  
 530 535 540  
 Thr Ser Pro Glu Cys Leu Gln Arg Thr Gly Ile Ser Leu Asn Ile Pro  
 545 550 555 560  
 Ala Pro Gln Pro Val Cys Ile Ser Glu Lys Gln Glu Asn Asp Val Ile  
 565 570 575  
 Asn Ala Ile Leu Lys Gln His Thr Glu Glu Lys Glu Phe Val Glu Lys  
 580 585 590  
 His Phe Asn Asp Leu Asn Met Lys Ala Val Glu Gln Asp Glu Pro Ile  
 595 600 605  
 Pro Gln Lys Pro Gln Ser Ala Phe Tyr Tyr Cys Arg Leu Leu Leu Ser  
 610 615 620  
 Ile Leu Gly Met Asn Ser Trp Asp Lys Arg Arg Ser Phe His Leu Leu  
 625 630 635 640  
 Lys Lys Asn Glu Lys Leu Leu Arg Glu Leu Arg Asn Leu Asp Ser Arg  
 645 650 655  
 Gln Cys Arg Glu Thr His Lys Ile Ala Val Phe Tyr Val Ala Glu Gly  
 660 665 670  
 Gln Glu Asp Lys His Ser Ile Leu Thr Asn Thr Gly Gly Ser Gln Ala  
 675 680 685  
 Tyr Glu Asp Phe Val Ala Gly Leu Gly Trp Glu Val Asn Leu Thr Asn  
 690 695 700  
 His Cys Gly Phe Met Gly Gly Leu Gln Lys Asn Lys Ser Thr Gly Leu  
 705 710 715 720  
 Thr Thr Pro Tyr Phe Ala Thr Ser Thr Val Glu Val Ile Phe His Val  
 725 730 735  
 Ser Thr Arg Met Pro Ser Asp Ser Asp Asp Ser Leu Thr Lys Lys Leu  
 740 745 750  
 Arg His Leu Gly Asn Asp Glu Val His Ile Val Trp Ser Glu His Thr  
 755 760 765  
 Arg Asp Tyr Arg Arg Gly Ile Ile Pro Thr Glu Phe Gly Asp Val Leu  
 770 775 780



Ile Val Ile Tyr Pro Met Lys Asn His Met Phe Ser Ile Gln Ile Met  
785 790 795 800

Lys Lys Pro Glu Val Pro Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile  
805 810 815

Val Asn Gly Lys Val Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn  
820 825 830

Ala Ser Arg Ala Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe Tyr  
835 840 845

Glu Glu Arg Ala Arg Tyr Leu Gln Thr Ile Val Gln His His Leu Glu  
850 855 860

Pro Thr Thr Phe Glu Asp Phe Ala Ala Gln Val Phe Ser Pro Ala Pro  
865 870 875 880

Tyr His His Leu Pro Ser Asp Ala Asp His  
885 890

<210> 166  
<211> 864  
<212> PRT  
<213> Homo sapiens

<400> 166

Gln Val Gln His Gly Ser Asn Val Asn Ile His Arg Leu Val Glu Gly  
1 5 10 15

Asn Val Val Ile Trp Glu Asn Ala Ser Thr Pro Leu Tyr Thr Gly Ala  
20 25 30

Ile Val Thr Asn Asn Asp Gly Pro Tyr Met Ala Tyr Val Glu Val Leu  
35 40 45

Gly Asp Pro Asn Leu Gln Phe Phe Ile Lys Ser Gly Asp Ala Trp Val  
50 55 60

Thr Leu Ser Glu His Glu Tyr Leu Ala Lys Leu Gln Glu Ile Arg Gln  
65 70 75 80

Ala Val His Ile Glu Ser Val Phe Ser Leu Asn Met Ala Phe Gln Leu  
85 90 95

Glu Asn Asn Lys Tyr Glu Val Glu Thr His Ala Lys Asn Gly Ala Asn  
100 105 110

Met Val Thr Phe Ile Pro Arg Asn Gly His Ile Cys Lys Met Val Tyr

115                      120                      125  
 His Lys Asn Val Arg Ile Tyr Lys Ala Thr Gly Asn Asp Thr Val Thr  
     130                      135                      140  
 Ser Val Val Gly Phe Phe Arg Gly Leu Arg Leu Leu Ile Asn Val  
     145                      150                      155                      160  
 Phe Ser Ile Asp Asp Asn Gly Met Met Ser Asn Arg Tyr Phe Gln His  
                     165                      170                      175  
 Val Asp Asp Lys Tyr Val Pro Ile Ser Gln Lys Asn Tyr Glu Thr Gly  
                     180                      185                      190  
 Ile Val Lys Leu Lys Asp Tyr Lys His Ala Tyr His Pro Val Asp Leu  
                     195                      200                      205  
 Asp Ile Lys Asp Ile Asp Tyr Thr Met Phe His Leu Ala Asp Ala Thr  
     210                      215                      220  
 Tyr His Glu Pro Cys Phe Lys Ile Ile Pro Asn Thr Gly Phe Cys Ile  
     225                      230                      235                      240  
 Thr Lys Leu Phe Asp Gly Asp Gln Val Leu Tyr Glu Ser Phe Asn Pro  
                     245                      250                      255  
 Leu Ile His Cys Ile Asn Glu Val His Ile Tyr Asp Arg Asn Asn Gly  
                     260                      265                      270  
 Ser Ile Ile Cys Leu His Leu Asn Tyr Ser Pro Pro Ser Tyr Lys Ala  
                     275                      280                      285  
 Tyr Leu Val Leu Lys Asp Thr Gly Trp Glu Ala Thr Thr His Pro Leu  
     290                      295                      300  
 Leu Glu Glu Lys Ile Glu Glu Leu Gln Asp Gln Arg Ala Cys Glu Leu  
     305                      310                      315                      320  
 Asp Val Asn Phe Ile Ser Asp Lys Asp Leu Tyr Val Ala Ala Leu Thr  
                     325                      330                      335  
 Asn Ala Asp Leu Asn Tyr Thr Met Val Thr Pro Arg Pro His Arg Asp  
                     340                      345                      350  
 Val Ile Arg Val Ser Asp Gly Ser Glu Val Leu Trp Tyr Tyr Glu Gly  
                     355                      360                      365  
 Leu Asp Asn Phe Leu Val Cys Ala Trp Ile Tyr Val Ser Asp Gly Val

370 375 380  
 Ala Ser Leu Val His Leu Arg Ile Lys Asp Arg Ile Pro Ala Asn Asn  
 385 390 395 400  
 Asp Ile Tyr Val Leu Lys Gly Asp Leu Tyr Trp Thr Arg Ile Thr Lys  
 405 410 415  
 Ile Gln Phe Thr Gln Glu Ile Lys Arg Leu Val Lys Lys Ser Lys Lys  
 420 425 430  
 Lys Leu Ala Pro Ile Thr Glu Glu Asp Ser Asp Lys His Asp Glu Pro  
 435 440 445  
 Pro Glu Gly Pro Gly Ala Ser Gly Leu Pro Pro Lys Ala Pro Gly Asp  
 450 455 460  
 Lys Glu Gly Ser Glu Gly His Lys Gly Pro Ser Lys Gly Ser Asp Ser  
 465 470 475 480  
 Ser Lys Glu Gly Lys Lys Pro Gly Ser Gly Lys Lys Pro Gly Pro Ala  
 485 490 495  
 Arg Glu His Lys Pro Ser Lys Ile Pro Thr Leu Ser Lys Lys Pro Ser  
 500 505 510  
 Gly Pro Lys Asp Pro Lys His Pro Arg Asp Pro Lys Glu Pro Arg Lys  
 515 520 525  
 Ser Lys Ser Pro Arg Thr Ala Ser Pro Thr Arg Arg Pro Ser Pro Lys  
 530 535 540  
 Leu Pro Gln Leu Ser Lys Leu Pro Lys Ser Thr Ser Pro Arg Ser Pro  
 545 550 555 560  
 Pro Pro Pro Thr Arg Pro Ser Ser Pro Glu Arg Pro Glu Gly Thr Lys  
 565 570 575  
 Ile Ile Lys Thr Ser Lys Pro Pro Ser Pro Lys Pro Pro Phe Asp Pro  
 580 585 590  
 Ser Phe Lys Glu Lys Phe Tyr Asp Asp Tyr Ser Lys Ala Ala Ser Arg  
 595 600 605  
 Ser Lys Glu Thr Lys Thr Thr Val Val Leu Asp Glu Ser Phe Glu Ser  
 610 615 620  
 Ile Leu Lys Glu Thr Leu Pro Glu Thr Pro Gly Thr Pro Phe Thr Thr

625                      630                      635                      640  
 Pro Arg Pro Val Pro Pro Lys Arg Pro Arg Thr Pro Glu Ser Pro Phe  
                                  645                                   650                                   655  
 Glu Pro Pro Lys Asp Pro Asp Ser Pro Ser Thr Ser Pro Ser Glu Phe  
                                  660                                   665                                   670  
 Phe Thr Pro Pro Glu Ser Lys Arg Thr Arg Phe His Glu Thr Pro Ala  
                                  675                                   680                                   685  
 Asp Thr Pro Leu Pro Asp Val Thr Ala Glu Leu Phe Lys Glu Pro Asp  
                                  690                                   695                                   700  
 Val Thr Ala Glu Thr Lys Ser Pro Asp Glu Ala Met Lys Arg Pro Arg  
                                  705                                   710                                   715                                   720  
 Ser Pro Ser Glu Tyr Glu Asp Thr Ser Pro Gly Asp Tyr Pro Ser Leu  
                                  725                                   730                                   735  
 Pro Met Lys Arg His Arg Leu Glu Arg Leu Arg Leu Thr Thr Thr Glu  
                                  740                                   745                                   750  
 Met Glu Thr Asp Pro Gly Arg Met Ala Lys Asp Ala Ser Gly Lys Pro  
                                  755                                   760                                   765  
 Val Lys Leu Lys Arg Ser Lys Ser Phe Asp Asp Leu Thr Thr Val Glu  
                                  770                                   775                                   780  
 Leu Ala Pro Glu Pro Lys Ala Ser Arg Ile Val Val Asp Asp Glu Gly  
                                  785                                   790                                   795                                   800  
 Thr Glu Ala Asp Asp Glu Glu Thr His Pro Pro Glu Glu Arg Gln Lys  
                                  805                                   810                                   815  
 Thr Glu Val Arg Arg Arg Arg Pro Pro Lys Lys Pro Ser Lys Ser Pro  
                                  820                                   825                                   830  
 Arg Pro Ser Lys Pro Lys Lys Pro Lys Lys Pro Asp Ser Ala Tyr Ile  
                                  835                                   840                                   845  
 Pro Ser Ile Leu Ala Ile Leu Val Val Ser Leu Ile Val Gly Ile Leu  
                                  850                                   855                                   860

<210> 167  
 <211> 339  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 167

Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn  
 1 5 10 15  
 Ala Arg Ser Arg Pro Ser Phe His Pro Val Ser Asp Glu Leu Val Asn  
 20 25 30  
 Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr  
 35 40 45  
 Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly  
 50 55 60  
 Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu  
 65 70 75 80  
 Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile  
 85 90 95  
 Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly  
 100 105 110  
 Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His  
 115 120 125  
 Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser  
 130 135 140  
 Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn  
 145 150 155 160  
 Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His  
 165 170 175  
 Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn  
 180 185 190  
 Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser  
 195 200 205  
 Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His  
 210 215 220  
 Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met  
 225 230 235 240  
 Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr  
 245 250 255

Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly  
260 265 270

Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu  
275 280 285

Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp  
290 295 300

Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly  
305 310 315 320

Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp  
325 330 335

Glu Lys Ile

<210> 168  
<211> 472  
<212> PRT  
<213> Homo sapiens

<400> 168

Met Lys Ser Ile Leu Asp Gly Leu Ala Asp Thr Thr Phe Arg Thr Ile  
1 5 10 15

Thr Thr Asp Leu Leu Tyr Val Gly Ser Asn Asp Ile Gln Tyr Glu Asp  
20 25 30

Ile Lys Gly Asp Met Ala Ser Lys Leu Gly Tyr Phe Pro Gln Lys Phe  
35 40 45

Pro Leu Thr Ser Phe Arg Gly Ser Pro Phe Gln Glu Lys Met Thr Ala  
50 55 60

Gly Asp Asn Pro Gln Leu Val Pro Ala Asp Gln Val Asn Ile Thr Glu  
65 70 75 80

Phe Tyr Asn Lys Ser Leu Ser Ser Phe Lys Glu Asn Glu Glu Asn Ile  
85 90 95

Gln Cys Gly Glu Asn Phe Met Asp Ile Glu Cys Phe Met Val Leu Asn  
100 105 110

Pro Ser Gln Gln Leu Ala Ile Ala Val Leu Ser Leu Thr Leu Gly Thr  
115 120 125

phe Thr Val Leu Glu Asn Leu Leu Val Leu Cys Val Ile Leu His Ser  
 130 135 140  
 Arg Ser Leu Arg Cys Arg Pro Ser Tyr His Phe Ile Gly Ser Leu Ala  
 145 150 155 160  
 Val Ala Asp Leu Leu Gly Ser Val Ile Phe Val Tyr Ser Phe Ile Asp  
 165 170 175  
 phe His Val Phe His Arg Lys Asp Ser Arg Asn Val Phe Leu Phe Lys  
 180 185 190  
 Leu Gly Gly Val Thr Ala Ser Phe Thr Ala Ser Val Gly Ser Leu Phe  
 195 200 205  
 Leu Thr Ala Ile Asp Arg Tyr Ile Ser Ile His Arg Pro Leu Ala Tyr  
 210 215 220  
 Lys Arg Ile Val Thr Arg Pro Lys Ala Val Val Ala Phe Cys Leu Met  
 225 230 235 240  
 Trp Thr Ile Ala Ile Val Ile Ala Val Leu Pro Leu Leu Gly Trp Asn  
 245 250 255  
 Cys Glu Lys Leu Gln Ser Val Cys Ser Asp Ile Phe Pro His Ile Asp  
 260 265 270  
 Glu Thr Tyr Leu Met Phe Trp Ile Gly Val Thr Ser Val Leu Leu Leu  
 275 280 285  
 Phe Ile Val Tyr Ala Tyr Met Tyr Ile Leu Trp Lys Ala His Ser His  
 290 295 300  
 Ala Val Arg Met Ile Gln Arg Gly Thr Gln Lys Ser Ile Ile Ile His  
 305 310 315 320  
 Thr Ser Glu Asp Gly Lys Val Gln Val Thr Arg Pro Asp Gln Ala Arg  
 325 330 335  
 Met Asp Ile Arg Leu Ala Lys Thr Leu Val Leu Ile Leu Val Val Leu  
 340 345 350  
 Ile Ile Cys Trp Gly Pro Leu Leu Ala Ile Met Val Tyr Asp Val Phe  
 355 360 365  
 Gly Lys Met Asn Lys Leu Ile Lys Thr Val Phe Ala Phe Cys Ser Met  
 370 375 380

Leu Cys Leu Leu Asn Ser Thr Val Asn Pro Ile Ile Tyr Ala Leu Arg  
385 390 395 400

Ser Lys Asp Leu Arg His Ala Phe Arg Ser Met Phe Pro Ser Cys Glu  
405 410 415

Gly Thr Ala Gln Pro Leu Asp Asn Ser Met Gly Asp Ser Asp Cys Leu  
420 425 430

His Lys His Ala Asn Asn Ala Ala Ser Val His Arg Ala Ala Glu Ser  
435 440 445

Cys Ile Lys Ser Thr Val Lys Ile Ala Lys Val Thr Met Ser Val Ser  
450 455 460

Thr Asp Thr Ser Ala Glu Ala Leu  
465 470

<210> 169  
<211> 426  
<212> PRT  
<213> Homo sapiens

<400> 169

Ala Gly Glu Asp Cys Gly Glu Glu Val Pro Thr Ile Glu Gly Met Arg  
1 5 10 15

Met His Leu Leu Glu Glu Thr Thr Val Arg Thr Glu Trp Thr Pro Ala  
20 25 30

Pro Gly Pro Val Asp Ala Tyr Glu Ile Gln Phe Ile Pro Thr Thr Glu  
35 40 45

Gly Ala Ser Pro Pro Phe Thr Ala Arg Val Pro Ser Ser Ala Ser Ala  
50 55 60

Tyr Asp Gln Arg Gly Leu Ala Pro Gly Gln Glu His Gln Val Thr Val  
65 70 75 80

Arg Ala Leu Arg Gly Thr Ser Trp Gly Leu Pro Ala Ser Lys Thr Val  
85 90 95

Thr Thr Met Ile Asp Gly Pro Gln Asp Leu Arg Val Val Ala Val Thr  
100 105 110

Pro Thr Thr Leu Glu Leu Gly Trp Leu Arg Pro Gln Ala Glu Val Asp  
115 120 125



Arg Phe Val Val Ser Tyr Val Ser Ala Asp Asn Gln Arg Val Arg Leu  
130 135 140

Glu Val Pro Pro Glu Ala Asp Gly Thr Leu Leu Thr Asp Leu Met Pro  
145 150 155 160

Gly Val Glu Tyr Val Val Thr Val Thr Ala Glu Arg Gly Arg Ala Val  
165 170 175

Ser Tyr Pro Ala Ser Val Arg Ala Asn Thr Gly Ser Ser Pro Leu Gly  
180 185 190

Leu Leu Gly Thr Thr Asp Glu Pro Pro Pro Ser Gly Pro Ser Thr Thr  
195 200 205

Gln Gly Ala Gln Ala Pro Leu Leu Gln Gln Arg Pro Gln Glu Leu Gly  
210 215 220

Glu Leu Arg Val Leu Gly Arg Asp Glu Thr Gly Arg Leu Arg Val Val  
225 230 235 240

Trp Thr Ala Gln Pro Asp Thr Phe Ala Tyr Phe Gln Leu Arg Met Arg  
245 250 255

Val Pro Glu Gly Pro Gly Ala His Glu Glu Val Leu Pro Gly Asp Val  
260 265 270

Arg Gln Ala Leu Val Pro Pro Pro Pro Gly Thr Pro Tyr Glu Leu  
275 280 285

Ser Leu His Gly Val Pro Pro Gly Gly Lys Pro Ser Asp Pro Ile Ile  
290 295 300

Tyr Gln Gly Ile Met Asp Lys Asp Glu Glu Lys Pro Gly Lys Ser Ser  
305 310 315 320

Gly Pro Pro Arg Leu Gly Glu Leu Thr Val Thr Asp Arg Thr Ser Asp  
325 330 335

Ser Leu Leu Leu Arg Trp Thr Val Pro Glu Gly Glu Phe Asp Ser Phe  
340 345 350

Val Ile Gln Tyr Lys Asp Arg Asp Gly Gln Pro Gln Val Val Pro Val  
355 360 365

Glu Gly Pro Gln Arg Ser Ala Val Ile Thr Ser Leu Asp Pro Gly Arg  
370 375 380

Lys Tyr Lys Phe Val Leu Tyr Gly Phe Val Gly Lys Lys Arg His Gly  
385 390 395 400

Pro Leu Val Ala Glu Ala Lys Ile Leu Pro Gln Ser Asp Pro Ser Pro  
405 410 415

Gly Thr Pro Pro Arg Leu Gly Asn Leu Trp  
420 425

<210> 170  
<211> 664  
<212> PRT  
<213> Homo sapiens

<400> 170

Met Glu Gly Phe Met Asp Ser Gly Thr Gln Thr Asp Ala Val Val Val  
1 5 10 15

Leu Ser Leu Ala Gln Ala Ala Val Leu Gly Leu Val Ser Glu Asn Glu  
20 25 30

Leu Phe Gly Ala Thr Ile Ser Ala Glu Ala Phe Tyr Pro Asp Leu Gly  
35 40 45

Pro Glu Leu Ser Gly Ala Ala Met Gly Glu Pro Glu Pro Pro Gly Pro  
50 55 60

Asp Val Tyr Gln Leu Ala Cys Asn Gly Arg Ala Leu Glu Glu Pro Ala  
65 70 75 80

Glu Glu Glu Val Leu Glu Val Glu Ala Ala Cys Glu Lys His Thr Arg  
85 90 95

Arg Lys Thr Arg Pro Pro Val Arg Leu Val Pro Lys Val Lys Phe Glu  
100 105 110

Lys Val Glu Glu Glu Glu Gln Glu Val Tyr Glu Val Ser Val Pro Gly  
115 120 125

Asp Asp Lys Asp Ala Gly Pro Ala Glu Ala Pro Ala Glu Ala Ala Ser  
130 135 140

Gly Gly Cys Asp Ala Leu Val Gln Ser Ser Ala Val Lys Met Ile Asp  
145 150 155 160

Leu Ser Ala Phe Ser Arg Lys Pro Arg Thr Leu Arg His Leu Pro Arg  
165 170 175

Thr Pro Arg Pro Glu Leu Asn Val Ala Pro Tyr Asp Pro His Phe Pro

180 185 190  
 Ala Pro Ala Arg Asp Gly Phe Pro Glu Pro Ser Met Ala Leu Pro Gly  
 195 200 205  
 Pro Glu Ala Leu Pro Thr Glu Cys Gly Phe Glu Pro Pro His Leu Ala  
 210 215 220  
 Pro Leu Ser Asp Pro Glu Ala Pro Ser Met Glu Ser Pro Glu Pro Val  
 225 230 235 240  
 Lys Pro Glu Gln Gly Phe Val Trp Gln Glu Ala Ser Glu Phe Glu Ala  
 245 250 255  
 Asp Thr Ala Gly Ser Thr Val Glu Arg His Lys Lys Ala Gln Leu Asp  
 260 265 270  
 Arg Leu Asp Ile Asn Val Gln Ile Asp Asp Ser Tyr Leu Val Glu Ala  
 275 280 285  
 Gly Asp Arg Gln Lys Arg Trp Gln Cys Arg Met Cys Glu Lys Ser Tyr  
 290 295 300  
 Thr Ser Lys Tyr Asn Leu Val Thr His Ile Leu Gly His Asn Gly Ile  
 305 310 315 320  
 Lys Pro His Ser Cys Pro His Cys Ser Lys Leu Phe Lys Gln Pro Ser  
 325 330 335  
 His Leu Gln Thr His Leu Leu Thr His Gln Gly Thr Arg Pro His Lys  
 340 345 350  
 Cys Gln Val Cys His Lys Ala Phe Thr Gln Thr Ser His Leu Lys Arg  
 355 360 365  
 His Met Leu Leu His Ser Glu Val Lys Pro Tyr Ser Cys His Phe Cys  
 370 375 380  
 Gly Arg Gly Phe Ala Tyr Pro Ser Glu Leu Lys Ala His Glu Val Lys  
 385 390 395 400  
 His Glu Ser Gly Arg Cys His Val Cys Val Glu Cys Gly Leu Asp Phe  
 405 410 415  
 Ser Thr Leu Thr Gln Leu Lys Arg His Leu Ala Ser His Gln Gly Pro  
 420 425 430  
 Thr Leu Tyr Gln Cys Leu Glu Cys Asp Lys Ser Phe His Tyr Arg Ser

435                      440                      445  
 Gln Leu Gln Asn His Met Leu Lys His Gln Asn Val Arg Pro Phe Val  
     450                      455                      460  
 Cys Thr Glu Cys Gly Met Glu Phe Ser Gln Ile His His Leu Lys Gln  
     465                      470                      475                      480  
 His Ser Leu Thr His Lys Gly Val Lys Glu Phe Lys Cys Glu Val Cys  
                             485                      490                      495  
 Gly Arg Glu Phe Thr Leu Gln Ala Asn Met Lys Arg His Met Leu Ile  
                             500                      505                      510  
 His Thr Ser Val Arg Pro Tyr Gln Cys His Ile Cys Phe Lys Thr Phe  
                             515                      520                      525  
 Val Gln Lys Gln Thr Leu Lys Thr His Met Ile Val His Ser Pro Val  
     530                      535                      540  
 Lys Pro Phe Lys Cys Lys Val Cys Gly Lys Ser Phe Asn Arg Met Tyr  
     545                      550                      555                      560  
 Asn Leu Leu Gly His Met His Leu His Ala Gly Ser Lys Pro Phe Lys  
                             565                      570                      575  
 Cys Pro Tyr Cys Ser Ser Lys Phe Asn Leu Lys Gly Asn Leu Ser Arg  
                             580                      585                      590  
 His Met Lys Val Lys His Gly Val Ile Asp Ile Gly Leu Asp Ser Gln  
                             595                      600                      605  
 Asp Pro Met Met Glu Leu Thr Gly Thr Asp Pro Ser Glu Leu Asp Gly  
     610                      615                      620  
 Gln Gln Glu Met Glu Asp Phe Glu Glu Asn Ala Tyr Ser Tyr Ala Ser  
     625                      630                      635                      640  
 Val Asp Ser Ser Ala Glu Ala Ser Val Leu Thr Glu Gln Ala Met Lys  
                             645                      650                      655  
 Glu Met Ala Tyr Tyr Asn Val Leu  
                             660

<210> 171  
 <211> 1028  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 171

Met Asp Ser Ala Leu Thr Ala Arg Asp Arg Val Gly Val Gln Asp Phe  
 1 5 10 15

Val Leu Leu Glu Asn Phe Thr Ser Glu Ala Ala Phe Ile Glu Asn Leu  
 20 25 30

Arg Arg Arg Phe Arg Glu Asn Leu Ile Tyr Thr Tyr Ile Gly Pro Val  
 35 40 45

Leu Val Ser Val Asn Pro Tyr Arg Asp Leu Gln Ile Tyr Ser Arg Gln  
 50 55 60

His Met Glu Arg Tyr Arg Gly Val Ser Phe Tyr Glu Val Pro Pro His  
 65 70 75 80

Leu Phe Ala Val Ala Asp Thr Val Tyr Arg Ala Leu Arg Thr Glu Arg  
 85 90 95

Arg Asp Gln Ala Val Met Ile Ser Gly Glu Ser Gly Ala Gly Lys Thr  
 100 105 110

Glu Ala Thr Lys Lys Leu Leu Gln Phe Tyr Ala Glu Thr Cys Pro Ala  
 115 120 125

Pro Gln Arg Gly Gly Ala Val Arg Asp Arg Leu Leu Gln Ser Asn Pro  
 130 135 140

Val Leu Glu Ala Phe Gly Asn Ala Lys Thr Leu Arg Asn Asp Asn Ser  
 145 150 155 160

Ser Arg Phe Gly Lys Tyr Met Asp Val Gln Phe Asp Phe Lys Gly Ala  
 165 170 175

Pro Val Gly Gly His Ile Leu Ser Tyr Leu Leu Glu Lys Ser Arg Val  
 180 185 190

Val His Gln Asn His Gly Glu Arg Asn Phe His Ile Phe Tyr Gln Leu  
 195 200 205

Leu Glu Gly Gly Glu Glu Glu Thr Leu Arg Arg Leu Gly Leu Glu Arg  
 210 215 220

Asn Pro Gln Ser Tyr Leu Tyr Leu Val Lys Gly Gln Cys Ala Lys Val  
 225 230 235 240

Ser Ser Ile Asn Asp Lys Ser Asp Trp Lys Val Val Arg Lys Ala Leu  
 245 250 255

Thr Val Ile Asp Phe Thr Glu Asp Glu Val Glu Asp Leu Leu Ser Ile  
 260 265 270  
 Val Ala Ser Val Leu His Leu Gly Asn Ile His Phe Ala Ala Asn Glu  
 275 280 285  
 Asp Ser Asn Ala Gln Val Thr Thr Glu Asn Gln Leu Lys Tyr Leu Thr  
 290 295 300  
 Arg Leu Leu Ser Val Glu Gly Ser Thr Leu Arg Glu Ala Leu Thr His  
 305 310 315 320  
 Arg Lys Ile Ile Ala Lys Gly Glu Glu Leu Leu Ser Pro Leu Asn Leu  
 325 330 335  
 Glu Gln Ala Ala Tyr Ala Arg Asn Ala Leu Ala Lys Ala Val Tyr Ser  
 340 345 350  
 Arg Thr Phe Thr Trp Leu Val Gly Lys Ile Asn Arg Ser Leu Ala Ser  
 355 360 365  
 Lys Asp Val Glu Ser Pro Ser Trp Arg Ser Thr Thr Val Leu Gly Leu  
 370 375 380  
 Leu Asp Ile Tyr Gly Phe Glu Val Phe Gln His Asn Ser Phe Glu Gln  
 385 390 395 400  
 Phe Cys Ile Asn Tyr Cys Asn Glu Lys Leu Gln Gln Leu Phe Ile Glu  
 405 410 415  
 Leu Pro Leu Lys Ser Glu Gln Glu Glu Tyr Glu Ala Glu Gly Ile Ala  
 420 425 430  
 Trp Glu Pro Val Gln Tyr Phe Asn Asn Lys Ile Ile Cys Asp Leu Val  
 435 440 445  
 Glu Glu Lys Phe Lys Gly Ile Ile Ser Ile Leu Asp Glu Glu Cys Leu  
 450 455 460  
 Arg Pro Gly Glu Ala Thr Asp Leu Thr Phe Leu Glu Lys Leu Glu Asp  
 465 470 475 480  
 Thr Val Lys His His Pro His Phe Leu Thr His Lys Leu Ala Asp Gln  
 485 490 495  
 Arg Thr Arg Lys Ser Leu Gly Arg Gly Glu Phe Arg Leu Leu His Tyr  
 500 505 510

Ala Gly Glu Val Thr Tyr Ser Val Thr Gly Phe Leu Asp Lys Asn Asn  
 515 520 525  
 Asp Leu Leu Phe Arg Asn Leu Lys Glu Thr Met Cys Ser Ser Lys Asn  
 530 535 540  
 Pro Ile Met Ser Gln Cys Phe Asp Arg Ser Glu Leu Ser Asp Lys Lys  
 545 550 555 560  
 Arg Pro Glu Thr Val Ala Thr Gln Phe Lys Met Ser Leu Leu Gln Leu  
 565 570 575  
 Val Glu Ile Leu Gln Ser Lys Glu Pro Ala Tyr Val Arg Cys Ile Lys  
 580 585 590  
 Pro Asn Asp Ala Lys Gln Pro Gly Arg Phe Asp Glu Val Leu Ile Arg  
 595 600 605  
 His Gln Val Lys Tyr Leu Gly Leu Leu Glu Asn Leu Arg Val Arg Arg  
 610 615 620  
 Ala Gly Phe Ala Tyr Arg Arg Lys Tyr Glu Ala Phe Leu Gln Arg Tyr  
 625 630 635 640  
 Lys Ser Leu Cys Pro Glu Thr Trp Pro Thr Trp Ala Gly Arg Pro Gln  
 645 650 655  
 Asp Gly Val Ala Val Leu Val Arg His Leu Gly Tyr Lys Pro Glu Glu  
 660 665 670  
 Tyr Lys Met Gly Arg Thr Lys Ile Phe Ile Arg Phe Pro Lys Thr Leu  
 675 680 685  
 Phe Ala Thr Glu Asp Ala Leu Glu Val Arg Arg Gln Ser Leu Ala Thr  
 690 695 700  
 Lys Ile Gln Ala Ala Trp Arg Gly Phe His Trp Arg Gln Lys Phe Leu  
 705 710 715 720  
 Arg Val Lys Arg Ser Ala Ile Cys Ile Gln Ser Trp Trp Arg Gly Thr  
 725 730 735  
 Leu Gly Arg Arg Lys Ala Ala Lys Arg Lys Trp Ala Ala Gln Thr Ile  
 740 745 750  
 Arg Arg Leu Ile Arg Gly Phe Ile Leu Arg His Ala Pro Arg Cys Pro  
 755 760 765

Glu Asn Ala Phe Phe Leu Asp His Val Arg Thr Ser Phe Leu Leu Asn  
 770 775 780  
 Leu Arg Arg Gln Leu Pro Arg Asn Val Leu Asp Thr Tyr Trp Pro Thr  
 785 790 795 800  
 Pro Pro Pro Ala Leu Arg Glu Ala Ser Glu Leu Leu Arg Glu Leu Cys  
 805 810 815  
 Ile Lys Asn Met Val Trp Lys Tyr Cys Arg Ser Ile Ser Pro Glu Trp  
 820 825 830  
 Lys Gln Gln Leu Gln Gln Lys Ala Val Ala Ser Glu Ile Phe Lys Gly  
 835 840 845  
 Lys Lys Asp Asn Tyr Pro Gln Ser Val Pro Arg Leu Phe Ile Ser Thr  
 850 855 860  
 Arg Leu Gly Thr Asp Glu Ile Ser Pro Arg Val Leu Gln Ala Leu Gly  
 865 870 875 880  
 Ser Glu Pro Ile Gln Tyr Ala Val Pro Val Val Lys Tyr Asp Arg Lys  
 885 890 895  
 Gly Tyr Lys Pro Arg Ser Arg Gln Leu Leu Leu Thr Pro Asn Ala Val  
 900 905 910  
 Val Ile Val Glu Asp Ala Lys Val Lys Gln Arg Ile Asp Tyr Ala Asn  
 915 920 925  
 Leu Thr Gly Ile Ser Val Ser Ser Leu Ser Asp Ser Leu Phe Val Leu  
 930 935 940  
 His Val Gln Arg Ala Asp Ile Lys Gln Lys Gly Asp Val Val Leu Gln  
 945 950 955 960  
 Ser Asp His Val Ile Glu Thr Leu Thr Lys Thr Ala Leu Ser Ala Asn  
 965 970 975  
 Arg Val Asn Ser Ile Asn Ile Asn Gln Gly Ser Ile Thr Phe Ala Gly  
 980 985 990  
 Gly Pro Gly Arg Asp Gly Thr Ile Asp Phe Thr Pro Gly Ser Glu Leu  
 995 1000 1005  
 Leu Ile Thr Lys Ala Lys Asn Gly His Leu Ala Val Val Ala Pro  
 1010 1015 1020



Arg Leu Asn Tyr Arg  
1025

<210> 172  
<211> 2426  
<212> PRT  
<213> Homo sapiens

<400> 172

Met Ala Thr Asn Ile Glu Gln Ile Phe Arg Ser Phe Val Val Ser Lys  
1 5 10 15

Phe Arg Glu Ile Gln Gln Glu Leu Ser Ser Gly Arg Asn Glu Gly Gln  
20 25 30

Leu Asn Gly Glu Thr Asn Thr Pro Ile Glu Gly Asn Gln Ala Gly Asp  
35 40 45

Ala Ala Ala Ser Ala Arg Ser Leu Pro Asn Glu Glu Ile Val Gln Lys  
50 55 60

Ile Glu Glu Val Leu Ser Gly Val Leu Asp Thr Glu Leu Arg Tyr Lys  
65 70 75 80

Pro Asp Leu Lys Glu Gly Ser Arg Lys Ser Arg Cys Val Ser Val Gln  
85 90 95

Thr Asp Pro Thr Asp Glu Ile Pro Thr Lys Lys Ser Lys Lys His Lys  
100 105 110

Lys His Lys Asn Lys Lys Lys Lys Lys Lys Glu Lys Glu Lys Lys  
115 120 125

Tyr Lys Arg Gln Pro Glu Glu Ser Glu Ser Lys Thr Lys Ser His Asp  
130 135 140

Asp Gly Asn Ile Asp Leu Glu Ser Asp Ser Phe Leu Lys Phe Asp Ser  
145 150 155 160

Glu Pro Ser Ala Val Ala Leu Glu Leu Pro Thr Arg Ala Phe Gly Pro  
165 170 175

Ser Glu Thr Asn Glu Ser Pro Ala Val Val Leu Glu Pro Pro Val Val  
180 185 190

Ser Met Glu Val Ser Glu Pro His Ile Leu Glu Thr Leu Lys Pro Ala  
195 200 205

Thr Lys Thr Ala Glu Leu Ser Val Val Ser Thr Ser Val Ile Ser Glu  
 210 215 220  
 Gln Ser Glu Gln Ser Val Ala Val Met Pro Glu Pro Ser Met Thr Lys  
 225 230 235 240  
 Ile Leu Asp Ser Phe Ala Ala Ala Pro Val Pro Thr Thr Thr Leu Val  
 245 250 255  
 Leu Lys Ser Ser Glu Pro Val Val Thr Met Ser Val Glu Tyr Gln Met  
 260 265 270  
 Lys Ser Val Leu Lys Ser Val Glu Ser Thr Ser Pro Glu Pro Ser Lys  
 275 280 285  
 Ile Met Leu Val Glu Pro Pro Val Ala Lys Val Leu Glu Pro Ser Glu  
 290 295 300  
 Thr Leu Val Val Ser Ser Glu Thr Pro Thr Glu Val Tyr Pro Glu Pro  
 305 310 315 320  
 Ser Thr Ser Thr Thr Met Asp Phe Pro Glu Ser Ser Ala Ile Glu Ala  
 325 330 335  
 Leu Arg Leu Pro Glu Gln Pro Val Asp Val Pro Ser Glu Ile Ala Asp  
 340 345 350  
 Ser Ser Met Thr Arg Pro Gln Glu Leu Pro Glu Leu Pro Lys Thr Thr  
 355 360 365  
 Ala Leu Glu Leu Gln Glu Ser Ser Val Ala Ser Ala Met Glu Leu Pro  
 370 375 380  
 Gly Pro Pro Ala Thr Ser Met Pro Glu Leu Gln Gly Pro Pro Val Thr  
 385 390 395 400  
 Pro Val Leu Glu Leu Pro Gly Pro Ser Ala Thr Pro Val Pro Glu Leu  
 405 410 415  
 Pro Gly Pro Leu Ser Thr Pro Val Pro Glu Leu Pro Gly Pro Pro Ala  
 420 425 430  
 Thr Ala Val Pro Glu Leu Pro Gly Pro Ser Val Thr Pro Val Pro Gln  
 435 440 445  
 Leu Ser Gln Glu Leu Pro Gly Leu Pro Ala Pro Ser Met Gly Leu Glu  
 450 455 460

Pro Pro Gln Glu Val Pro Glu Pro Ser Val Met Ala Gln Glu Leu Pro  
 465 470 475 480  
 Gly Leu Pro Leu Val Thr Ala Ala Val Glu Leu Pro Glu Gln Pro Ala  
 485 490 495  
 Val Thr Val Ala Met Glu Leu Thr Glu Gln Pro Val Thr Thr Thr Glu  
 500 505 510  
 Leu Glu Gln Pro Val Gly Met Thr Thr Val Glu His Pro Gly His Pro  
 515 520 525  
 Glu Val Thr Thr Ala Thr Gly Leu Leu Gly Gln Pro Glu Ala Thr Met  
 530 535 540  
 Val Leu Glu Leu Pro Gly Gln Pro Val Ala Thr Thr Ala Leu Glu Leu  
 545 550 555 560  
 Pro Gly Gln Pro Ser Val Thr Gly Val Pro Glu Leu Pro Gly Leu Pro  
 565 570 575  
 Ser Ala Thr Arg Ala Leu Glu Leu Ser Gly Gln Pro Val Ala Thr Gly  
 580 585 590  
 Ala Leu Glu Leu Pro Gly Pro Leu Met Ala Ala Gly Ala Leu Glu Phe  
 595 600 605  
 Ser Gly Gln Ser Gly Ala Ala Gly Ala Leu Glu Leu Leu Gly Gln Pro  
 610 615 620  
 Leu Ala Thr Gly Val Leu Glu Leu Pro Gly Gln Pro Gly Ala Pro Glu  
 625 630 635 640  
 Leu Pro Gly Gln Pro Val Ala Thr Val Ala Leu Glu Ile Ser Val Gln  
 645 650 655  
 Ser Val Val Thr Thr Ser Glu Leu Ser Thr Met Thr Val Ser Gln Ser  
 660 665 670  
 Leu Glu Val Pro Ser Thr Thr Ala Leu Glu Ser Tyr Asn Thr Val Ala  
 675 680 685  
 Gln Glu Leu Pro Thr Thr Leu Val Gly Glu Thr Ser Val Thr Val Gly  
 690 695 700  
 Val Asp Pro Leu Met Ala Pro Glu Ser His Ile Leu Ala Ser Asn Thr  
 705 710 715 720

Met Glu Thr His Ile Leu Ala Ser Asn Thr Met Asp Ser Gln Met Leu  
 725 730 735  
 Ala Ser Asn Thr Met Asp Ser Gln Met Leu Ala Ser Asn Thr Met Asp  
 740 745 750  
 Ser Gln Met Leu Ala Ser Ser Thr Met Asp Ser Gln Met Leu Ala Thr  
 755 760 765  
 Ser Ser Met Asp Ser Gln Met Leu Ala Thr Ser Ser Met Asp Ser Gln  
 770 775 780  
 Met Leu Ala Thr Ser Thr Met Asp Ser Gln Met Leu Ala Thr Ser Ser  
 785 790 795 800  
 Met Asp Ser Gln Met Leu Ala Thr Ser Ser Met Asp Ser Gln Met Leu  
 805 810 815  
 Ala Thr Ser Ser Met Asp Ser Gln Met Leu Ala Thr Ser Ser Met Asp  
 820 825 830  
 Ser Gln Met Leu Ala Thr Ser Thr Met Asp Ser Gln Met Leu Ala Thr  
 835 840 845  
 Ser Thr Met Asp Ser Gln Met Leu Ala Thr Ser Ser Met Asp Ser Gln  
 850 855 860  
 Met Leu Ala Ser Gly Thr Met Asp Ser Gln Met Leu Ala Ser Gly Thr  
 865 870 875 880  
 Met Asp Ala Gln Met Leu Ala Ser Gly Thr Met Asp Ala Gln Met Leu  
 885 890 895  
 Ala Ser Ser Thr Gln Asp Ser Ala Met Leu Gly Ser Lys Ser Pro Asp  
 900 905 910  
 Pro Tyr Arg Leu Ala Gln Asp Pro Tyr Arg Leu Ala Gln Asp Pro Tyr  
 915 920 925  
 Arg Leu Gly His Asp Pro Tyr Arg Leu Gly His Asp Ala Tyr Arg Leu  
 930 935 940  
 Gly Gln Asp Pro Tyr Arg Leu Gly His Asp Pro Tyr Arg Leu Thr Pro  
 945 950 955 960  
 Asp Pro Tyr Arg Met Ser Pro Arg Pro Tyr Arg Ile Ala Pro Arg Ser  
 965 970 975

Tyr Arg Ile Ala Pro Arg Pro Tyr Arg Leu Ala Pro Arg Pro Leu Met  
 980 985 990

Leu Ala Ser Arg Arg Ser Met Met Met Ser Tyr Ala Ala Glu Arg Ser  
 995 1000 1005

Met Met Ser Ser Tyr Glu Arg Ser Met Met Ser Tyr Glu Arg Ser  
 1010 1015 1020

Met Met Ser Pro Met Ala Glu Arg Ser Met Met Ser Ala Tyr Glu  
 1025 1030 1035

Arg Ser Met Met Ser Ala Tyr Glu Arg Ser Met Met Ser Pro Met  
 1040 1045 1050

Ala Glu Arg Ser Met Met Ser Ala Tyr Glu Arg Ser Met Met Ser  
 1055 1060 1065

Ala Tyr Glu Arg Ser Met Met Ser Pro Met Ala Asp Arg Ser Met  
 1070 1075 1080

Met Ser Met Gly Ala Asp Arg Ser Met Met Ser Ser Tyr Ser Ala  
 1085 1090 1095

Ala Asp Arg Ser Met Met Ser Ser Tyr Ser Ala Ala Asp Arg Ser  
 1100 1105 1110

Met Met Ser Ser Tyr Thr Ala Asp Arg Ser Met Met Ser Met Ala  
 1115 1120 1125

Ala Asp Ser Tyr Thr Asp Ser Tyr Thr Asp Thr Tyr Thr Glu Ala  
 1130 1135 1140

Tyr Met Val Pro Pro Leu Pro Pro Glu Glu Pro Pro Thr Met Pro  
 1145 1150 1155

Pro Leu Pro Pro Glu Glu Pro Pro Met Thr Pro Pro Leu Pro Pro  
 1160 1165 1170

Glu Glu Pro Pro Glu Gly Pro Ala Leu Pro Thr Glu Gln Ser Ala  
 1175 1180 1185

Leu Thr Ala Glu Asn Thr Trp Pro Thr Glu Val Pro Ser Leu Pro  
 1190 1195 1200

Ser Glu Glu Ser Val Ser Gln Pro Glu Pro Pro Val Ser Gln Ser  
 1205 1210 1215

Glu Ile Ser Glu Pro Ser Ala Val Pro Thr Asp Tyr Ser Val Ser  
 1220 1225 1230  
 Ala Ser Asp Pro Ser Val Leu Val Ser Glu Ala Ala Val Thr Val  
 1235 1240 1245  
 Pro Glu Pro Pro Pro Glu Pro Glu Ser Ser Ile Thr Leu Thr Pro  
 1250 1255 1260  
 Val Glu Ser Ala Val Val Ala Glu Glu His Glu Val Val Pro Glu  
 1265 1270 1275  
 Arg Pro Val Thr Cys Met Val Ser Glu Thr Pro Ala Met Ser Ala  
 1280 1285 1290  
 Glu Pro Thr Val Leu Ala Ser Glu Pro Pro Val Met Ser Glu Thr  
 1295 1300 1305  
 Ala Glu Thr Phe Asp Ser Met Arg Ala Ser Gly His Val Ala Ser  
 1310 1315 1320  
 Glu Val Ser Thr Ser Leu Leu Val Pro Ala Val Thr Thr Pro Val  
 1325 1330 1335  
 Leu Ala Glu Ser Ile Leu Glu Pro Pro Ala Met Ala Ala Pro Glu  
 1340 1345 1350  
 Ser Ser Ala Met Ala Val Leu Glu Ser Ser Ala Val Thr Val Leu  
 1355 1360 1365  
 Glu Ser Ser Thr Val Thr Val Leu Glu Ser Ser Thr Val Thr Val  
 1370 1375 1380  
 Leu Glu Pro Ser Val Val Thr Val Pro Glu Pro Pro Val Val Ala  
 1385 1390 1395  
 Glu Pro Asp Tyr Val Thr Ile Pro Val Pro Val Val Ser Ala Leu  
 1400 1405 1410  
 Glu Pro Ser Val Pro Val Leu Glu Pro Ala Val Ser Val Leu Gln  
 1415 1420 1425  
 Pro Ser Met Ile Val Ser Glu Pro Ser Val Ser Val Gln Glu Ser  
 1430 1435 1440  
 Thr Val Thr Val Ser Glu Pro Ala Val Thr Val Ser Glu Gln Thr  
 1445 1450 1455

Gln Val Ile Pro Thr Glu Val Ala Ile Glu Ser Thr Pro Met Ile  
 1460 1465 1470  
 Leu Glu Ser Ser Ile Met Ser Ser His Val Met Lys Gly Ile Asn  
 1475 1480 1485  
 Leu Ser Ser Gly Asp Gln Asn Leu Ala Pro Glu Ile Gly Met Gln  
 1490 1495 1500  
 Glu Ile Ala Leu His Ser Gly Glu Glu Pro His Ala Glu Glu His  
 1505 1510 1515  
 Leu Lys Gly Asp Phe Tyr Glu Ser Glu His Gly Ile Asn Ile Asp  
 1520 1525 1530  
 Leu Asn Ile Asn Asn His Leu Ile Ala Lys Glu Met Glu His Asn  
 1535 1540 1545  
 Thr Val Cys Ala Ala Gly Thr Ser Pro Val Gly Glu Ile Gly Glu  
 1550 1555 1560  
 Glu Lys Ile Leu Pro Thr Ser Glu Thr Lys Gln Arg Thr Val Leu  
 1565 1570 1575  
 Asp Thr Tyr Pro Gly Val Ser Glu Ala Asp Ala Gly Glu Thr Leu  
 1580 1585 1590  
 Ser Ser Thr Gly Pro Phe Ala Leu Glu Pro Asp Ala Thr Gly Thr  
 1595 1600 1605  
 Ser Lys Gly Ile Glu Phe Thr Thr Ala Ser Thr Leu Ser Leu Val  
 1610 1615 1620  
 Asn Lys Tyr Asp Val Asp Leu Ser Leu Thr Thr Gln Asp Thr Glu  
 1625 1630 1635  
 His Asp Met Val Ile Ser Thr Ser Pro Ser Gly Gly Ser Glu Ala  
 1640 1645 1650  
 Asp Ile Glu Gly Pro Leu Pro Ala Lys Asp Ile His Leu Asp Leu  
 1655 1660 1665  
 Pro Ser Asn Asn Asn Leu Val Ser Lys Asp Thr Glu Glu Pro Leu  
 1670 1675 1680  
 Pro Val Lys Glu Ser Asp Gln Thr Leu Ala Ala Leu Leu Ser Pro  
 1685 1690 1695

Lys Glu Ser Ser Gly Gly Glu Lys Glu Val Pro Pro Pro Pro Lys  
 1700 1705 1710  
 Glu Thr Leu Pro Asp Ser Gly Phe Ser Ala Asn Ile Glu Asp Ile  
 1715 1720 1725  
 Asn Glu Ala Asp Leu Val Arg Pro Leu Leu Pro Lys Asp Met Glu  
 1730 1735 1740  
 Arg Leu Thr Ser Leu Arg Ala Gly Ile Glu Gly Pro Leu Leu Ala  
 1745 1750 1755  
 Ser Asp Val Gly Arg Asp Arg Ser Ala Ala Ser Pro Val Val Ser  
 1760 1765 1770  
 Ser Met Pro Glu Arg Ala Ser Glu Ser Ser Ser Glu Glu Lys Asp  
 1775 1780 1785  
 Asp Tyr Glu Ile Phe Val Lys Val Lys Asp Thr His Glu Lys Ser  
 1790 1795 1800  
 Lys Lys Asn Lys Asn Arg Asp Lys Gly Glu Lys Glu Lys Lys Arg  
 1805 1810 1815  
 Asp Ser Ser Leu Arg Ser Arg Ser Lys Arg Ser Lys Ser Ser Glu  
 1820 1825 1830  
 His Lys Ser Arg Lys Arg Thr Ser Glu Ser Arg Ser Arg Ala Arg  
 1835 1840 1845  
 Lys Arg Ser Ser Lys Ser Lys Ser His Arg Ser Gln Thr Arg Ser  
 1850 1855 1860  
 Arg Ser Arg Ser Arg Arg Arg Arg Arg Ser Ser Arg Ser Arg Ser  
 1865 1870 1875  
 Lys Ser Arg Gly Arg Arg Ser Val Ser Lys Glu Lys Arg Lys Arg  
 1880 1885 1890  
 Ser Pro Lys His Arg Ser Lys Ser Arg Glu Arg Lys Arg Lys Arg  
 1895 1900 1905  
 Ser Ser Ser Arg Asp Asn Arg Lys Thr Val Arg Ala Arg Ser Arg  
 1910 1915 1920  
 Thr Pro Ser Arg Arg Ser Arg Ser His Thr Pro Ser Arg Arg Arg  
 1925 1930 1935



Arg Ser Arg Ser Val Gly Arg Arg Arg Ser Phe Ser Ile Ser Pro  
 1940 1945 1950  
 Ser Arg Arg Ser Arg Thr Pro Ser Arg Arg Ser Arg Thr Pro Ser  
 1955 1960 1965  
 Arg Arg Ser Arg Thr Pro Ser Arg Arg Ser Arg Thr Pro Ser Arg  
 1970 1975 1980  
 Arg Ser Arg Thr Pro Ser Arg Arg Ser Arg Thr Pro Ser Arg Arg  
 1985 1990 1995  
 Arg Arg Ser Arg Ser Val Val Arg Arg Arg Ser Phe Ser Ile Ser  
 2000 2005 2010  
 Pro Val Arg Leu Arg Arg Ser Arg Thr Pro Leu Arg Arg Arg Phe  
 2015 2020 2025  
 Ser Arg Ser Pro Ile Arg Arg Lys Arg Ser Arg Ser Ser Glu Arg  
 2030 2035 2040  
 Gly Arg Ser Pro Lys Arg Leu Thr Asp Leu Asp Lys Ala Gln Leu  
 2045 2050 2055  
 Leu Glu Ile Ala Lys Ala Asn Ala Ala Ala Met Cys Ala Lys Ala  
 2060 2065 2070  
 Gly Val Pro Leu Pro Pro Asn Leu Lys Pro Ala Pro Pro Pro Thr  
 2075 2080 2085  
 Ile Glu Glu Lys Val Ala Lys Lys Ser Gly Gly Ala Thr Ile Glu  
 2090 2095 2100  
 Glu Leu Thr Glu Lys Cys Lys Gln Ile Ala Gln Ser Lys Glu Asp  
 2105 2110 2115  
 Asp Asp Val Ile Val Asn Lys Pro His Val Ser Asp Glu Glu Glu  
 2120 2125 2130  
 Glu Glu Pro Pro Phe Tyr His His Pro Phe Lys Leu Ser Glu Pro  
 2135 2140 2145  
 Lys Pro Ile Phe Phe Asn Leu Asn Ile Ala Ala Ala Lys Pro Thr  
 2150 2155 2160  
 Pro Pro Lys Ser Gln Val Thr Leu Thr Lys Glu Phe Pro Val Ser  
 2165 2170 2175

Ser Gly Ser Gln His Arg Lys Lys Glu Ala Asp Ser Val Tyr Gly  
 2180 2185 2190  
 Glu Trp Val Pro Val Glu Lys Asn Gly Glu Glu Asn Lys Asp Asp  
 2195 2200 2205  
 Asp Asn Val Phe Ser Ser Asn Leu Pro Ser Glu Pro Val Asp Ile  
 2210 2215 2220  
 Ser Thr Ala Met Ser Glu Arg Ala Leu Ala Gln Lys Arg Leu Ser  
 2225 2230 2235  
 Glu Asn Ala Phe Asp Leu Glu Ala Met Ser Met Leu Asn Arg Ala  
 2240 2245 2250  
 Gln Glu Arg Ile Asp Ala Trp Ala Gln Leu Asn Ser Ile Pro Gly  
 2255 2260 2265  
 Gln Phe Thr Gly Ser Thr Gly Val Gln Val Leu Thr Gln Glu Gln  
 2270 2275 2280  
 Leu Ala Asn Thr Gly Ala Gln Ala Trp Ile Lys Lys Asp Gln Phe  
 2285 2290 2295  
 Leu Arg Ala Ala Pro Val Thr Gly Gly Met Gly Ala Val Leu Met  
 2300 2305 2310  
 Arg Lys Met Gly Trp Arg Glu Gly Glu Gly Leu Gly Lys Asn Lys  
 2315 2320 2325  
 Glu Gly Asn Lys Glu Pro Ile Leu Val Asp Phe Lys Thr Asp Arg  
 2330 2335 2340  
 Lys Gly Leu Val Ala Val Gly Glu Arg Ala Gln Lys Arg Ser Gly  
 2345 2350 2355  
 Asn Phe Ser Ala Ala Met Lys Asp Leu Ser Gly Lys His Pro Val  
 2360 2365 2370  
 Ser Ala Leu Met Glu Ile Cys Asn Lys Arg Arg Trp Gln Pro Pro  
 2375 2380 2385  
 Glu Phe Leu Leu Val His Asp Ser Gly Pro Asp His Arg Lys His  
 2390 2395 2400  
 Phe Leu Phe Arg Val Leu Arg Asn Gly Ala Leu Thr Arg Pro Asn  
 2405 2410 2415

Cys Met Phe Phe Leu Asn Arg Tyr  
2420 2425

<210> 173  
<211> 957  
<212> PRT  
<213> Homo sapiens

<400> 173

Met Arg Pro Gly Thr Gly Ala Glu Arg Gly Gly Leu Met Val Ser Glu  
1 5 10 15

Met Glu Ser His Pro Pro Ser Gln Gly Pro Gly Asp Gly Glu Arg Arg  
20 25 30

Leu Ser Gly Ser Ser Leu Cys Ser Gly Ser Trp Val Ser Ala Asp Gly  
35 40 45

Phe Leu Arg Arg Arg Pro Ser Met Gly His Pro Gly Met His Tyr Ala  
50 55 60

Pro Met Gly Met His Pro Met Gly Gln Arg Ala Asn Met Pro Pro Val  
65 70 75 80

Pro His Gly Met Met Pro Gln Met Met Pro Pro Met Gly Gly Pro Pro  
85 90 95

Met Gly Gln Met Pro Gly Met Met Ser Ser Val Met Pro Gly Met Met  
100 105 110

Met Ser His Met Ser Gln Ala Ser Met Gln Pro Ala Leu Pro Pro Gly  
115 120 125

Val Asn Ser Met Asp Val Ala Ala Gly Thr Ala Ser Gly Ala Lys Ser  
130 135 140

Met Trp Thr Glu His Lys Ser Pro Asp Gly Arg Thr Tyr Tyr Tyr Asn  
145 150 155 160

Thr Glu Thr Lys Gln Ser Thr Trp Glu Lys Pro Asp Asp Leu Lys Thr  
165 170 175

Pro Ala Glu Gln Leu Leu Ser Lys Cys Pro Trp Lys Glu Tyr Lys Ser  
180 185 190

Asp Ser Gly Lys Pro Tyr Tyr Tyr Asn Ser Gln Thr Lys Glu Ser Arg  
195 200 205

Trp Ala Lys Pro Lys Glu Leu Glu Asp Leu Glu Gly Tyr Gln Asn Thr  
 210 215 220  
 Ile Val Ala Gly Ser Leu Ile Thr Lys Ser Asn Leu His Ala Met Ile  
 225 230 235 240  
 Lys Ala Glu Glu Ser Ser Lys Gln Glu Glu Cys Thr Thr Thr Ser Thr  
 245 250 255  
 Ala Pro Val Pro Thr Thr Glu Ile Pro Thr Thr Met Ser Thr Met Ala  
 260 265 270  
 Ala Ala Glu Ala Ala Ala Ala Val Val Ala Ala Ala Ala Ala Ala Ala  
 275 280 285  
 Ala Ala Ala Ala Ala Ala Asn Ala Asn Ala Ser Thr Ser Ala Ser Asn  
 290 295 300  
 Thr Val Ser Gly Thr Val Pro Val Val Pro Glu Pro Glu Val Thr Ser  
 305 310 315 320  
 Ile Val Ala Thr Val Val Asp Asn Glu Asn Thr Val Thr Ile Ser Thr  
 325 330 335  
 Glu Glu Gln Ala Gln Leu Thr Ser Thr Pro Ala Ile Gln Asp Gln Ser  
 340 345 350  
 Val Glu Val Ser Ser Asn Thr Gly Glu Glu Thr Ser Lys Gln Glu Thr  
 355 360 365  
 Val Ala Asp Phe Thr Pro Lys Lys Glu Glu Glu Glu Ser Gln Pro Ala  
 370 375 380  
 Lys Lys Thr Tyr Thr Trp Asn Thr Lys Glu Glu Ala Lys Gln Ala Phe  
 385 390 395 400  
 Lys Glu Leu Leu Lys Glu Lys Arg Val Pro Ser Asn Ala Ser Trp Glu  
 405 410 415  
 Gln Ala Met Lys Met Ile Ile Asn Asp Pro Arg Tyr Ser Ala Leu Ala  
 420 425 430  
 Lys Leu Ser Glu Lys Lys Gln Ala Phe Asn Ala Tyr Lys Val Gln Thr  
 435 440 445  
 Glu Lys Glu Glu Lys Glu Glu Ala Arg Ser Lys Tyr Lys Glu Ala Lys  
 450 455 460

465                      470                      475                      480  
 Thr Arg Tyr Lys Lys Ala Glu Gln Met Phe Gly Glu Met Glu Val Trp  
                                  485                                   490                                   495  
 Asn Ala Ile Ser Glu Arg Asp Arg Leu Glu Ile Tyr Glu Asp Val Leu  
                                  500                                   505                                   510  
 Phe Phe Leu Ser Lys Lys Glu Lys Glu Gln Ala Lys Gln Leu Arg Lys  
                                  515                                   520                                   525  
 Arg Asn Trp Glu Ala Leu Lys Asn Ile Leu Asp Asn Met Ala Asn Val  
                                  530                                   535                                   540  
 Thr Tyr Ser Thr Thr Trp Ser Glu Ala Gln Gln Tyr Leu Met Asp Asn  
                                  545                                   550                                   555                                   560  
 Pro Thr Phe Ala Glu Asp Glu Glu Leu Gln Asn Met Asp Lys Glu Asp  
                                  565                                   570                                   575  
 Ala Leu Ile Cys Phe Glu Glu His Ile Arg Ala Leu Glu Lys Glu Glu  
                                  580                                   585                                   590  
 Glu Glu Glu Lys Gln Lys Ser Leu Leu Arg Glu Arg Arg Arg Gln Arg  
                                  595                                   600                                   605  
 Lys Asn Arg Glu Ser Phe Gln Ile Phe Leu Asp Glu Leu His Glu His  
                                  610                                   615                                   620  
 Gly Gln Leu His Ser Met Ser Ser Trp Met Glu Leu Tyr Pro Thr Ile  
                                  625                                   630                                   635                                   640  
 Ser Ser Asp Ile Arg Phe Thr Asn Met Leu Gly Gln Pro Gly Ser Thr  
                                  645                                   650                                   655  
 Ala Leu Asp Leu Phe Lys Phe Tyr Val Glu Asp Leu Lys Ala Arg Tyr  
                                  660                                   665                                   670  
 His Asp Glu Lys Lys Ile Ile Lys Asp Ile Leu Lys Asp Lys Gly Phe  
                                  675                                   680                                   685  
 Val Val Glu Val Asn Thr Thr Phe Glu Asp Phe Val Ala Ile Ile Ser  
                                  690                                   695                                   700  
 Ser Thr Lys Arg Ser Thr Thr Leu Asp Ala Gly Asn Ile Lys Leu Ala  
                                  705                                   710                                   715                                   720

Phe Asn Ser Leu Leu Glu Lys Ala Glu Ala Arg Glu Arg Glu Arg Glu  
725 730 735

Lys Glu Glu Ala Arg Lys Met Lys Arg Lys Glu Ser Ala Phe Lys Ser  
740 745 750

Met Leu Lys Gln Ala Ala Pro Pro Ile Glu Leu Asp Ala Val Trp Glu  
755 760 765

Asp Ile Arg Glu Arg Phe Val Lys Glu Pro Ala Phe Glu Asp Ile Thr  
770 775 780

Leu Glu Ser Glu Arg Lys Arg Ile Phe Lys Asp Phe Met His Val Leu  
785 790 795 800

Glu His Glu Cys Gln His His His Ser Lys Asn Lys Lys His Ser Lys  
805 810 815

Lys Ser Lys Lys His His Arg Lys Arg Ser Arg Ser Arg Ser Gly Ser  
820 825 830

Asp Ser Asp Asp Asp Asp Ser His Ser Lys Lys Lys Arg Gln Arg Ser  
835 840 845

Glu Ser Arg Ser Ala Ser Glu His Ser Ser Ser Ala Glu Ser Glu Arg  
850 855 860

Ser Tyr Lys Lys Ser Lys Lys His Lys Lys Lys Ser Lys Lys Arg Arg  
865 870 875 880

His Lys Ser Asp Ser Pro Glu Ser Asp Ala Glu Arg Glu Lys Asp Lys  
885 890 895

Lys Glu Lys Asp Arg Glu Ser Glu Lys Asp Arg Thr Arg Gln Arg Ser  
900 905 910

Glu Ser Lys His Lys Ser Pro Lys Lys Lys Thr Gly Lys Asp Ser Gly  
915 920 925

Asn Trp Asp Thr Ser Gly Ser Glu Leu Ser Glu Gly Glu Leu Glu Lys  
930 935 940

Arg Arg Arg Thr Leu Leu Glu Gln Leu Asp Asp Asp Gln  
945 950 955

<210> 174  
<211> 125  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 174

Met Glu Ser Lys Glu Lys Leu Ala Val Asn Ser Leu Ser Met Glu Asn  
1 5 10 15

Ala Asn Gln Glu Asn Glu Glu Lys Glu Gln Val Ala Asn Lys Gly Glu  
20 25 30

Pro Leu Ala Leu Pro Leu Asp Ala Gly Glu Tyr Cys Val Pro Arg Gly  
35 40 45

Asn Arg Arg Arg Phe Arg Val Arg Gln Pro Ile Leu Gln Tyr Arg Trp  
50 55 60

Asp Met Met His Arg Leu Gly Glu Pro Gln Ala Arg Met Arg Glu Glu  
65 70 75 80

Asn Met Glu Arg Ile Gly Glu Gly Val Arg Gln Leu Met Glu Lys Leu  
85 90 95

Arg Glu Lys Gln Leu Ser His Ser Leu Arg Ala Val Ser Thr Asp Pro  
100 105 110

Pro His His Asp His His Asp Glu Phe Cys Leu Met Pro  
115 120 125

&lt;210&gt; 175

&lt;211&gt; 864

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 175

Gln Val Gln His Gly Ser Asn Val Asn Ile His Arg Leu Val Glu Gly  
1 5 10 15

Asn Val Val Ile Trp Glu Asn Ala Ser Thr Pro Leu Tyr Thr Gly Ala  
20 25 30

Ile Val Thr Asn Asn Asp Gly Pro Tyr Met Ala Tyr Val Glu Val Leu  
35 40 45

Gly Asp Pro Asn Leu Gln Phe Phe Ile Lys Ser Gly Asp Ala Trp Val  
50 55 60

Thr Leu Ser Glu His Glu Tyr Leu Ala Lys Leu Gln Glu Ile Arg Gln  
65 70 75 80

Ala Val His Ile Glu Ser Val Phe Ser Leu Asn Met Ala Phe Gln Leu  
85 90 95

Glu Asn Asn Lys Tyr Glu Val Glu Thr His Ala Lys Asn Gly Ala Asn  
 100 105 110  
 Met Val Thr Phe Ile Pro Arg Asn Gly His Ile Cys Lys Met Val Tyr  
 115 120 125  
 His Lys Asn Val Arg Ile Tyr Lys Ala Thr Gly Asn Asp Thr Val Thr  
 130 135 140  
 Ser Val Val Gly Phe Phe Arg Gly Leu Arg Leu Leu Leu Ile Asn Val  
 145 150 155 160  
 Phe Ser Ile Asp Asp Asn Gly Met Met Ser Asn Arg Tyr Phe Gln His  
 165 170 175  
 Val Asp Asp Lys Tyr Val Pro Ile Ser Gln Lys Asn Tyr Glu Thr Gly  
 180 185 190  
 Ile Val Lys Leu Lys Asp Tyr Lys His Ala Tyr His Pro Val Asp Leu  
 195 200 205  
 Asp Ile Lys Asp Ile Asp Tyr Thr Met Phe His Leu Ala Asp Ala Thr  
 210 215 220  
 Tyr His Glu Pro Cys Phe Lys Ile Ile Pro Asn Thr Gly Phe Cys Ile  
 225 230 235 240  
 Thr Lys Leu Phe Asp Gly Asp Gln Val Leu Tyr Glu Ser Phe Asn Pro  
 245 250 255  
 Leu Ile His Cys Ile Asn Glu Val His Ile Tyr Asp Arg Asn Asn Gly  
 260 265 270  
 Ser Ile Ile Cys Leu His Leu Asn Tyr Ser Pro Pro Ser Tyr Lys Ala  
 275 280 285  
 Tyr Leu Val Leu Lys Asp Thr Gly Trp Glu Ala Thr Thr His Pro Leu  
 290 295 300  
 Leu Glu Glu Lys Ile Glu Glu Leu Gln Asp Gln Arg Ala Cys Glu Leu  
 305 310 315 320  
 Asp Val Asn Phe Ile Ser Asp Lys Asp Leu Tyr Val Ala Ala Leu Thr  
 325 330 335  
 Asn Ala Asp Leu Asn Tyr Thr Met Val Thr Pro Arg Pro His Arg Asp  
 340 345 350



Val Ile Arg Val Ser Asp Gly Ser Glu Val Leu Trp Tyr Tyr Glu Gly  
 355 360 365  
 Leu Asp Asn Phe Leu Val Cys Ala Trp Ile Tyr Val Ser Asp Gly Val  
 370 375 380  
 Ala Ser Leu Val His Leu Arg Ile Lys Asp Arg Ile Pro Ala Asn Asn  
 385 390 395 400  
 Asp Ile Tyr Val Leu Lys Gly Asp Leu Tyr Trp Thr Arg Ile Thr Lys  
 405 410 415  
 Ile Gln Phe Thr Gln Glu Ile Lys Arg Leu Val Lys Lys Ser Lys Lys  
 420 425 430  
 Lys Leu Ala Pro Ile Thr Glu Glu Asp Ser Asp Lys His Asp Glu Pro  
 435 440 445  
 Pro Glu Gly Pro Gly Ala Ser Gly Leu Pro Pro Lys Ala Pro Gly Asp  
 450 455 460  
 Lys Glu Gly Ser Glu Gly His Lys Gly Pro Ser Lys Gly Ser Asp Ser  
 465 470 475 480  
 Ser Lys Glu Gly Lys Lys Pro Gly Ser Gly Lys Lys Pro Gly Pro Ala  
 485 490 495  
 Arg Glu His Lys Pro Ser Lys Ile Pro Thr Leu Ser Lys Lys Pro Ser  
 500 505 510  
 Gly Pro Lys Asp Pro Lys His Pro Arg Asp Pro Lys Glu Pro Arg Lys  
 515 520 525  
 Ser Lys Ser Pro Arg Thr Ala Ser Pro Thr Arg Arg Pro Ser Pro Lys  
 530 535 540  
 Leu Pro Gln Leu Ser Lys Leu Pro Lys Ser Thr Ser Pro Arg Ser Pro  
 545 550 555 560  
 Pro Pro Pro Thr Arg Pro Ser Ser Pro Glu Arg Pro Glu Gly Thr Lys  
 565 570 575  
 Ile Ile Lys Thr Ser Lys Pro Pro Ser Pro Lys Pro Pro Phe Asp Pro  
 580 585 590  
 Ser Phe Lys Glu Lys Phe Tyr Asp Asp Tyr Ser Lys Ala Ala Ser Arg  
 595 600 605

Ser Lys Glu Thr Lys Thr Thr Val Val Leu Asp Glu Ser Phe Glu Ser  
 610 615 620  
 Ile Leu Lys Glu Thr Leu Pro Glu Thr Pro Gly Thr Pro Phe Thr Thr  
 625 630 635 640  
 Pro Arg Pro Val Pro Pro Lys Arg Pro Arg Thr Pro Glu Ser Pro Phe  
 645 650 655  
 Glu Pro Pro Lys Asp Pro Asp Ser Pro Ser Thr Ser Pro Ser Glu Phe  
 660 665 670  
 Phe Thr Pro Pro Glu Ser Lys Arg Thr Arg Phe His Glu Thr Pro Ala  
 675 680 685  
 Asp Thr Pro Leu Pro Asp Val Thr Ala Glu Leu Phe Lys Glu Pro Asp  
 690 695 700  
 Val Thr Ala Glu Thr Lys Ser Pro Asp Glu Ala Met Lys Arg Pro Arg  
 705 710 715 720  
 Ser Pro Ser Glu Tyr Glu Asp Thr Ser Pro Gly Asp Tyr Pro Ser Leu  
 725 730 735  
 Pro Met Lys Arg His Arg Leu Glu Arg Leu Arg Leu Thr Thr Thr Glu  
 740 745 750  
 Met Glu Thr Asp Pro Gly Arg Met Ala Lys Asp Ala Ser Gly Lys Pro  
 755 760 765  
 Val Lys Leu Lys Arg Ser Lys Ser Phe Asp Asp Leu Thr Thr Val Glu  
 770 775 780  
 Leu Ala Pro Glu Pro Lys Ala Ser Arg Ile Val Val Asp Asp Glu Gly  
 785 790 795 800  
 Thr Glu Ala Asp Asp Glu Glu Thr His Pro Pro Glu Glu Arg Gln Lys  
 805 810 815  
 Thr Glu Val Arg Arg Arg Arg Pro Pro Lys Lys Pro Ser Lys Ser Pro  
 820 825 830  
 Arg Pro Ser Lys Pro Lys Lys Pro Lys Lys Pro Asp Ser Ala Tyr Ile  
 835 840 845  
 Pro Ser Ile Leu Ala Ile Leu Val Val Ser Leu Ile Val Gly Ile Leu  
 850 855 860

<210> 176  
 <211> 333  
 <212> PRT  
 <213> Homo sapiens

<400> 176

Met Ser Trp Ile Lys Glu Gly Glu Leu Ser Leu Trp Glu Arg Phe Cys  
 1 5 10 15

Ala Asn Ile Ile Lys Ala Gly Pro Met Pro Lys His Ile Ala Phe Ile  
 20 25 30

Met Asp Gly Asn Arg Arg Tyr Ala Lys Lys Cys Gln Val Glu Arg Gln  
 35 40 45

Glu Gly His Ser Gln Gly Phe Asn Lys Leu Ala Glu Thr Leu Arg Trp  
 50 55 60

Cys Leu Asn Leu Gly Ile Leu Glu Val Thr Val Tyr Ala Phe Ser Ile  
 65 70 75 80

Glu Asn Phe Lys Arg Ser Lys Ser Glu Val Asp Gly Leu Met Asp Leu  
 85 90 95

Ala Arg Gln Lys Phe Ser Arg Leu Met Glu Glu Lys Glu Lys Leu Gln  
 100 105 110

Lys His Gly Val Cys Ile Arg Val Leu Gly Asp Leu His Leu Leu Pro  
 115 120 125

Leu Asp Leu Gln Glu Leu Ile Ala Gln Ala Val Gln Ala Thr Lys Asn  
 130 135 140

Tyr Asn Lys Cys Phe Leu Asn Val Cys Phe Ala Tyr Thr Ser Arg His  
 145 150 155 160

Glu Ile Ser Asn Ala Val Arg Glu Met Ala Trp Gly Val Glu Gln Gly  
 165 170 175

Leu Leu Asp Pro Ser Asp Ile Ser Glu Ser Leu Leu Asp Lys Cys Leu  
 180 185 190

Tyr Thr Asn Arg Ser Pro His Pro Asp Ile Leu Ile Arg Thr Ser Gly  
 195 200 205

Glu Val Arg Leu Ser Asp Phe Leu Leu Trp Gln Thr Ser His Ser Cys  
 210 215 220

Leu Val Phe Gln Pro Val Leu Trp Pro Glu Tyr Inr Phe Trp Asn Leu  
225 230 235 240

Phe Glu Ala Ile Leu Gln Phe Gln Met Asn His Ser Val Leu Gln Lys  
245 250 255

Ala Arg Asp Met Tyr Ala Glu Glu Arg Lys Arg Gln Gln Leu Glu Arg  
260 265 270

Asp Gln Ala Thr Val Thr Glu Gln Leu Leu Arg Glu Gly Leu Gln Ala  
275 280 285

Ser Gly Asp Ala Gln Leu Arg Arg Thr Arg Leu His Lys Leu Ser Ala  
290 295 300

Arg Arg Glu Glu Arg Val Gln Gly Phe Leu Gln Ala Leu Glu Leu Lys  
305 310 315 320

Arg Ala Asp Trp Leu Ala Arg Leu Gly Thr Ala Ser Ala  
325 330

<210> 177  
<211> 897  
<212> PRT  
<213> Homo sapiens

<400> 177

Met Glu Tyr Thr Lys Gln Leu Ile Leu Ser Cys Leu Leu Asn Ile Cys  
1 5 10 15

Gln Lys Leu Ser Pro Asp Gly Gly Lys Ile Pro Lys Asp Ile Leu Asp  
20 25 30

Glu Glu Lys Phe Asn Val Glu Leu Ile Val Gln Cys Ile Arg Leu Ser  
35 40 45

Glu Met Pro Gln Thr His His His Ala Leu Leu Leu Leu Gly Thr Val  
50 55 60

Ala Gly Ile Phe Pro Asp Lys Val Leu His Asn Ile Met Ser Ile Phe  
65 70 75 80

Thr Phe Met Gly Ala Asn Val Met Arg Leu Asp Asp Thr Tyr Ser Phe  
85 90 95

Gln Val Ile Asn Lys Thr Val Lys Met Val Ile Pro Ala Leu Ile Gln  
100 105 110

Ser Asp Ser Gly Asp Ser Ile Glu Val Ser Arg Asn Val Glu Glu Ile  
 115 120 125  
 Val Val Lys Ile Ile Ser Val Phe Val Asp Ala Leu Pro His Val Pro  
 130 135 140  
 Glu His Arg Arg Leu Pro Ile Leu Val Gln Leu Val Asp Thr Leu Gly  
 145 150 155 160  
 Ala Glu Lys Phe Leu Trp Ile Leu Leu Ile Leu Leu Phe Glu Gln Tyr  
 165 170 175  
 Val Thr Lys Thr Val Leu Ala Ala Ala Tyr Gly Glu Lys Asp Ala Ile  
 180 185 190  
 Leu Glu Ala Asp Thr Glu Phe Trp Phe Ser Val Cys Cys Glu Phe Ser  
 195 200 205  
 Val Gln His Gln Ile Gln Ser Leu Met Asn Ile Leu Gln Tyr Leu Leu  
 210 215 220  
 Lys Leu Pro Glu Glu Lys Glu Glu Thr Ile Pro Lys Ala Val Ser Phe  
 225 230 235 240  
 Asn Lys Ser Glu Ser Gln Glu Glu Met Leu Gln Val Phe Asn Val Glu  
 245 250 255  
 Thr His Thr Ser Lys Gln Leu Arg His Phe Lys Phe Leu Ser Val Ser  
 260 265 270  
 Phe Met Ser Gln Leu Leu Ser Ser Asn Asp Phe Leu Lys Lys Val Val  
 275 280 285  
 Glu Ser Gly Gly Pro Glu Ile Leu Lys Gly Leu Glu Glu Arg Leu Leu  
 290 295 300  
 Glu Thr Val Leu Gly Tyr Ile Ser Ala Val Ala Gln Ser Met Glu Arg  
 305 310 315 320  
 Asn Ala Asp Lys Leu Thr Val Lys Phe Trp Arg Ala Leu Leu Ser Lys  
 325 330 335  
 Ala Tyr Asp Leu Leu Asp Lys Val Asn Ala Leu Leu Pro Thr Glu Thr  
 340 345 350  
 Phe Ile Pro Val Ile Arg Gly Leu Val Gly Asn Pro Leu Pro Ser Val  
 355 360 365

Arg Arg Lys Ala Leu Asp Leu Leu Asn Asn Lys Leu Gln Gln Asn Ile  
370 375 380

Ser Trp Lys Lys Thr Ile Val Thr Arg Phe Leu Lys Leu Val Pro Asp  
385 390 395 400

Leu Leu Ala Ile Val Gln Arg Lys Lys Lys Glu Gly Glu Glu Glu Gln  
405 410 415

Ala Ile Asn Arg Gln Thr Ala Leu Tyr Thr Leu Lys Leu Leu Cys Lys  
420 425 430

Asn Phe Gly Ala Glu Asn Pro Asp Pro Phe Val Pro Val Leu Ser Thr  
435 440 445

Ala Val Lys Leu Ile Ala Pro Glu Arg Lys Glu Glu Lys Asn Val Leu  
450 455 460

Gly Ser Ala Leu Leu Cys Ile Ala Glu Val Thr Ser Thr Leu Glu Ala  
465 470 475 480

Leu Ala Ile Pro Gln Leu Pro Ser Leu Met Pro Ser Leu Leu Thr Thr  
485 490 495

Met Lys Asn Thr Ser Glu Leu Val Ser Ser Glu Val Tyr Leu Leu Ser  
500 505 510

Ala Leu Ala Ala Leu Gln Lys Val Val Glu Thr Leu Pro His Phe Ile  
515 520 525

Ser Pro Tyr Leu Glu Gly Ile Leu Ser Gln Val Ile His Leu Glu Lys  
530 535 540

Ile Thr Ser Glu Met Gly Ser Ala Ser Arg Ala Asn Ile Arg Leu Thr  
545 550 555 560

Ser Leu Lys Lys Thr Leu Ala Thr Thr Leu Ala Pro Arg Val Leu Leu  
565 570 575

Pro Ala Ile Lys Lys Thr Tyr Lys Gln Ile Glu Lys Asn Trp Lys Asn  
580 585 590

His Met Gly Pro Phe Met Ser Ile Leu Gln Glu His Ile Gly Ala Met  
595 600 605

Lys Lys Glu Glu Leu Thr Ser His Gln Ser Gln Leu Thr Ala Phe Phe  
610 615 620

Leu Glu Ala Leu Asp Phe Arg Ala Gln His Ser Glu Asn Asp Leu Glu  
 625 630 635 640  
 Glu Val Gly Lys Thr Glu Asn Cys Ile Ile Asp Cys Leu Val Ala Met  
 645 650 655  
 Val Val Lys Leu Ser Glu Val Thr Phe Arg Pro Leu Phe Phe Lys Leu  
 660 665 670  
 Phe Asp Trp Ala Lys Thr Glu Asp Ala Pro Lys Asp Arg Leu Leu Thr  
 675 680 685  
 Phe Tyr Asn Leu Ala Asp Cys Ile Ala Glu Lys Leu Lys Gly Leu Phe  
 690 695 700  
 Thr Leu Phe Ala Gly His Leu Val Lys Pro Phe Ala Asp Thr Leu Asp  
 705 710 715 720  
 Gln Val Asn Ile Ser Lys Thr Asp Glu Ala Phe Phe Asp Ser Glu Asn  
 725 730 735  
 Asp Pro Glu Lys Cys Cys Leu Leu Leu Gln Phe Ile Leu Asn Cys Leu  
 740 745 750  
 Tyr Lys Ile Phe Leu Phe Asp Thr Gln His Phe Ile Ser Lys Glu Arg  
 755 760 765  
 Ala Gly Ala Leu Met Met Pro Leu Val Asp Gln Leu Val Asn Arg Leu  
 770 775 780  
 Gly Gly Glu Glu Lys Phe Gln Glu Arg Val Thr Lys His Leu Ile Pro  
 785 790 795 800  
 Cys Ile Ala Gln Phe Ser Val Ala Met Ala Asp Asp Ser Leu Trp Lys  
 805 810 815  
 Pro Leu Asn Tyr Gln Ile Leu Leu Lys Thr Arg Asp Ser Ser Pro Lys  
 820 825 830  
 Val Arg Phe Ala Ala Leu Ile Thr Val Leu Ala Leu Ala Glu Lys Leu  
 835 840 845  
 Lys Glu Asn Tyr Ile Val Leu Leu Pro Glu Ser Ile Pro Phe Leu Ala  
 850 855 860  
 Glu Leu Met Glu Asp Glu Cys Glu Glu Val Glu His Gln Cys Gln Lys  
 865 870 875 880

Thr Ile Gln Gln Leu Glu Thr Val Leu Gly Glu Pro Leu Gln Ser Tyr  
 885 890 895

Phe

<210> 178  
 <211> 104  
 <212> PRT  
 <213> Homo sapiens  
 <400> 178

Met Gly Gln Cys Arg Ser Ala Asn Ala Glu Asp Ala Gln Glu Phe Ser  
 1 5 10 15

Asp Val Glu Arg Ala Ile Glu Thr Leu Ile Lys Asn Phe His Gln Tyr  
 20 25 30

Ser Val Glu Gly Gly Lys Glu Thr Leu Thr Pro Ser Glu Leu Arg Asp  
 35 40 45

Leu Val Thr Gln Gln Leu Pro His Leu Met Pro Ser Asn Cys Gly Leu  
 50 55 60

Glu Glu Lys Ile Ala Asn Leu Gly Ser Cys Asn Asp Ser Lys Leu Glu  
 65 70 75 80

Phe Arg Ser Phe Trp Glu Leu Ile Gly Glu Ala Ala Lys Ser Val Lys  
 85 90 95

Leu Glu Arg Pro Val Arg Gly His  
 100

<210> 179  
 <211> 943  
 <212> PRT  
 <213> Homo sapiens  
 <400> 179

Met Gly Leu Thr Lys Gln Tyr Leu Arg Tyr Val Ala Ser Ala Val Phe  
 1 5 10 15

Gly Val Ile Gly Ser Gln Lys Gly Asn Ile Val Phe Val Thr Leu Arg  
 20 25 30

Gly Glu Lys Gly Arg Tyr Val Ala Val Pro Ala Cys Glu His Val Phe  
 35 40 45

Ile Trp Asp Leu Arg Lys Gly Glu Lys Ile Leu Ile Leu Gln Gly Leu  
 50 55 60



Lys Gln Glu Val Thr Cys Leu Cys Pro Ser Pro Asp Gly Leu His Leu  
 65 70 75 80  
 Ala Val Gly Tyr Glu Asp Gly Ser Ile Arg Ile Phe Ser Leu Leu Ser  
 85 90 95  
 Gly Glu Gly Asn Val Thr Phe Asn Gly His Lys Ala Ala Ile Thr Thr  
 100 105 110  
 Leu Lys Tyr Asp Gln Leu Gly Gly Arg Leu Ala Ser Gly Ser Lys Asp  
 115 120 125  
 Thr Asp Ile Ile Val Trp Asp Val Ile Asn Glu Ser Gly Leu Tyr Arg  
 130 135 140  
 Leu Lys Gly His Lys Asp Ala Ile Thr Gln Ala Leu Phe Leu Arg Glu  
 145 150 155 160  
 Lys Asn Leu Leu Val Thr Ser Gly Lys Asp Thr Met Val Lys Trp Trp  
 165 170 175  
 Asp Leu Asp Thr Gln His Cys Phe Lys Thr Met Val Gly His Arg Thr  
 180 185 190  
 Glu Val Trp Gly Leu Val Leu Leu Ser Glu Glu Lys Arg Leu Ile Thr  
 195 200 205  
 Gly Ala Ser Asp Ser Glu Leu Arg Val Trp Asp Ile Ala Tyr Leu Gln  
 210 215 220  
 Glu Ile Glu Asp Pro Glu Glu Pro Asp Pro Lys Lys Ile Lys Gly Ser  
 225 230 235 240  
 Ser Pro Gly Ile Gln Asp Thr Leu Glu Ala Glu Asp Gly Ala Phe Glu  
 245 250 255  
 Thr Asp Glu Ala Pro Glu Asp Arg Ile Leu Ser Cys Arg Lys Ala Gly  
 260 265 270  
 Ser Ile Met Arg Glu Gly Arg Asp Arg Val Val Asn Leu Ala Val Asp  
 275 280 285  
 Lys Thr Gly Arg Ile Leu Ala Cys His Gly Thr Asp Ser Val Leu Glu  
 290 295 300  
 Leu Phe Cys Ile Leu Ser Lys Lys Glu Ile Gln Lys Lys Met Asp Lys  
 305 310 315 320

Lys Met Lys Lys Ala Arg Lys Lys Ala Lys Leu His Ser Ser Lys Gly  
 325 330 335  
 Glu Glu Glu Asp Pro Glu Val Asn Val Glu Met Ser Leu Gln Asp Glu  
 340 345 350  
 Ile Gln Arg Val Thr Asn Ile Lys Thr Ser Ala Lys Ile Lys Ser Phe  
 355 360 365  
 Asp Leu Ile His Ser Pro His Gly Glu Leu Lys Ala Val Phe Leu Leu  
 370 375 380  
 Gln Asn Asn Leu Val Glu Leu Tyr Ser Leu Asn Pro Ser Leu Pro Thr  
 385 390 395 400  
 Pro Gln Pro Val Arg Thr Ser Arg Ile Thr Ile Gly Gly His Arg Ser  
 405 410 415  
 Asp Val Arg Thr Leu Ser Phe Ser Ser Asp Asn Ile Ala Val Leu Ser  
 420 425 430  
 Ala Ala Ala Asp Ser Ile Lys Ile Trp Asn Arg Ser Thr Leu Gln Cys  
 435 440 445  
 Ile Arg Thr Met Thr Cys Glu Tyr Ala Leu Cys Ser Phe Phe Val Pro  
 450 455 460  
 Gly Asp Arg Gln Val Val Ile Gly Thr Lys Thr Gly Lys Leu Gln Leu  
 465 470 475 480  
 Tyr Asp Leu Ala Ser Gly Asn Leu Leu Glu Thr Ile Asp Ala His Asp  
 485 490 495  
 Gly Ala Leu Trp Ser Met Ser Leu Ser Pro Asp Gln Arg Gly Phe Val  
 500 505 510  
 Thr Gly Gly Ala Asp Lys Ser Val Lys Phe Trp Asp Phe Glu Leu Val  
 515 520 525  
 Lys Asp Glu Asn Ser Thr Gln Lys Arg Leu Ser Val Lys Gln Thr Arg  
 530 535 540  
 Thr Leu Gln Leu Asp Glu Asp Val Leu Cys Val Ser Tyr Ser Pro Asn  
 545 550 555 560  
 Gln Lys Leu Leu Ala Val Ser Leu Leu Asp Cys Thr Val Lys Ile Phe  
 565 570 575

Tyr Val Asp Thr Leu Lys Phe Phe Leu Ser Leu Tyr Gly His Lys Leu  
580 585 590

Pro Val Ile Cys Met Asp Ile Ser His Asp Gly Ala Leu Ile Ala Thr  
595 600 605

Gly Ser Ala Asp Arg Asn Val Lys Ile Trp Gly Leu Asp Phe Gly Asp  
610 615 620

Cys His Lys Ser Leu Phe Ala His Asp Asp Ser Val Met Tyr Leu Gln  
625 630 635 640

Phe Val Pro Lys Ser His Leu Phe Phe Thr Ala Gly Lys Asp His Lys  
645 650 655

Ile Lys Gln Trp Asp Ala Asp Lys Phe Glu His Ile Gln Thr Leu Glu  
660 665 670

Gly His His Gln Glu Ile Trp Cys Leu Ala Val Ser Pro Ser Gly Asp  
675 680 685

Tyr Val Val Ser Ser Ser His Asp Lys Ser Leu Arg Leu Trp Glu Arg  
690 695 700

Thr Arg Glu Pro Leu Ile Leu Glu Glu Glu Arg Glu Met Glu Arg Glu  
705 710 715 720

Ala Glu Tyr Glu Glu Ser Val Ala Lys Glu Asp Gln Pro Ala Val Pro  
725 730 735

Gly Glu Thr Gln Gly Asp Ser Tyr Phe Thr Gly Lys Lys Thr Ile Glu  
740 745 750

Thr Val Lys Ala Ala Glu Arg Ile Met Glu Ala Ile Glu Leu Tyr Arg  
755 760 765

Glu Glu Thr Ala Lys Met Lys Glu His Lys Ala Ile Cys Lys Ala Ala  
770 775 780

Gly Lys Glu Val Pro Leu Pro Ser Asn Pro Ile Leu Met Ala Tyr Gly  
785 790 795 800

Ser Ile Ser Pro Ser Ala Tyr Val Leu Glu Ile Phe Lys Gly Ile Lys  
805 810 815

Ser Ser Glu Leu Glu Glu Ser Leu Leu Val Leu Pro Phe Ser Tyr Val  
820 825 830

Pro Asp Ile Leu Lys Leu Phe Asn Glu Phe Ile Gln Leu Gly Ser Asp  
835 840 845

Val Glu Leu Ile Cys Arg Cys Leu Phe Phe Leu Leu Arg Ile His Phe  
850 855 860

Gly Gln Ile Thr Ser Asn Gln Met Leu Val Pro Val Ile Glu Lys Leu  
865 870 875 880

Arg Glu Thr Thr Ile Ser Lys Val Ser Gln Val Arg Asp Val Ile Gly  
885 890 895

Phe Asn Met Ala Gly Leu Asp Tyr Leu Lys Arg Glu Cys Glu Ala Lys  
900 905 910

Ser Glu Val Met Phe Phe Ala Asp Ala Thr Ser His Leu Glu Glu Lys  
915 920 925

Lys Arg Lys Arg Lys Lys Arg Glu Lys Leu Ile Leu Thr Leu Thr  
930 935 940

<210> 180  
<211> 150  
<212> PRT  
<213> Homo sapiens

<400> 180

Ile Gly Ala Pro Arg Gly Arg Trp Leu His Ser Leu Gly Gly Gly Asp  
1 5 10 15

Gln Ser His Val Met Ser Val Val Arg Ser Ser Val His Ala Arg Trp  
20 25 30

Ile Val Gly Lys Val Ile Gly Thr Lys Met Gln Lys Thr Ala Lys Val  
35 40 45

Arg Val Thr Arg Leu Val Leu Asp Pro Tyr Leu Leu Lys Tyr Phe Asn  
50 55 60

Lys Arg Lys Thr Tyr Phe Ala His Asp Ala Leu Gln Gln Cys Thr Val  
65 70 75 80

Gly Asp Ile Val Leu Leu Arg Ala Leu Pro Val Pro Arg Ala Lys His  
85 90 95

Val Lys His Glu Leu Ala Glu Ile Val Phe Lys Val Gly Lys Val Ile  
100 105 110

Asp Pro Val Thr Gly Lys Pro Cys Ala Gly Thr Thr Tyr Leu Glu Ser  
115 120 125

Pro Leu Ser Ser Glu Thr Thr Gln Leu Ser Lys Asn Leu Glu Glu Leu  
130 135 140

Asn Ile Ser Ser Ala Gln  
145 150

<210> 181  
<211> 661  
<212> PRT  
<213> Homo sapiens

<400> 181

Met Glu Met Thr Glu Met Thr Gly Val Ser Leu Lys Arg Gly Ala Leu  
1 5 10 15

Val Val Glu Asp Asn Asp Ser Gly Val Pro Val Glu Glu Thr Lys Lys  
20 25 30

Gln Lys Leu Ser Glu Cys Ser Leu Thr Lys Gly Gln Asp Gly Leu Gln  
35 40 45

Asn Asp Phe Leu Ser Ile Ser Glu Asp Val Pro Arg Pro Pro Asp Thr  
50 55 60

Val Ser Thr Gly Lys Gly Gly Lys Asn Ser Glu Ala Gln Leu Glu Asp  
65 70 75 80

Glu Glu Glu Glu Glu Glu Asp Gly Leu Ser Glu Glu Cys Glu Glu Glu  
85 90 95

Glu Ser Glu Ser Phe Ala Asp Met Met Lys His Gly Leu Thr Glu Ala  
100 105 110

Asp Val Gly Ile Thr Lys Phe Val Ser Ser His Gln Gly Phe Ser Gly  
115 120 125

Ile Leu Lys Glu Arg Tyr Ser Asp Phe Val Val His Glu Ile Gly Lys  
130 135 140

Asp Gly Arg Ile Ser His Leu Asn Asp Leu Ser Ile Pro Val Asp Glu  
145 150 155 160

Glu Asp Pro Ser Glu Asp Ile Phe Thr Val Leu Thr Ala Glu Glu Lys  
165 170 175

180 185 190  
 Ala Ile Glu Val Ile Glu Asp Thr Lys Glu Lys Arg Thr Ile Ile His  
 195 200 205  
 Gln Ala Ile Lys Ser Leu Phe Pro Gly Leu Glu Thr Lys Thr Glu Asp  
 210 215 220  
 Arg Glu Gly Lys Lys Tyr Ile Val Ala Tyr His Ala Ala Gly Lys Lys  
 225 230 235 240  
 Ala Leu Ala Asn Pro Arg Lys His Ser Trp Pro Lys Ser Arg Gly Ser  
 245 250 255  
 Tyr Cys His Phe Val Leu Tyr Lys Glu Asn Lys Asp Thr Met Asp Ala  
 260 265 270  
 Ile Asn Val Leu Ser Lys Tyr Leu Arg Val Lys Pro Asn Ile Phe Ser  
 275 280 285  
 Tyr Met Gly Thr Lys Asp Lys Arg Ala Ile Thr Val Gln Glu Ile Ala  
 290 295 300  
 Val Leu Lys Ile Thr Ala Gln Arg Leu Ala His Leu Asn Lys Cys Leu  
 305 310 315 320  
 Met Asn Phe Lys Leu Gly Asn Phe Ser Tyr Gln Lys Asn Pro Leu Lys  
 325 330 335  
 Leu Gly Glu Leu Gln Gly Asn His Phe Thr Val Val Leu Arg Asn Ile  
 340 345 350  
 Thr Gly Thr Asp Asp Gln Val Gln Gln Ala Met Asn Ser Leu Lys Glu  
 355 360 365  
 Ile Gly Phe Ile Asn Tyr Tyr Gly Met Gln Arg Phe Gly Thr Thr Ala  
 370 375 380  
 Val Pro Thr Tyr Gln Val Gly Arg Ala Ile Leu Gln Asn Ser Trp Thr  
 385 390 395 400  
 Glu Val Met Asp Leu Ile Leu Lys Pro Arg Ser Gly Ala Glu Lys Gly  
 405 410 415  
 Tyr Leu Val Lys Cys Arg Glu Glu Trp Ala Lys Thr Lys Asp Pro Thr  
 420 425 430

Ala Ala Leu Arg Lys Leu Pro Val Lys Arg Cys Val Glu Gly Gln Leu  
 435 440 445

Leu Arg Gly Leu Ser Lys Tyr Gly Met Lys Asn Ile Val Ser Ala Phe  
 450 455 460

Gly Ile Ile Pro Arg Asn Asn Arg Leu Met Tyr Ile His Ser Tyr Gln  
 465 470 475 480

Ser Tyr Val Trp Asn Asn Met Val Ser Lys Arg Ile Glu Asp Tyr Gly  
 485 490 495

Leu Lys Pro Val Pro Gly Asp Leu Val Leu Lys Gly Ala Thr Ala Thr  
 500 505 510

Tyr Ile Glu Glu Asp Asp Val Asn Asn Tyr Ser Ile His Asp Val Val  
 515 520 525

Met Pro Leu Pro Gly Phe Asp Val Ile Tyr Pro Lys His Lys Ile Gln  
 530 535 540

Glu Ala Tyr Arg Glu Met Leu Thr Ala Asp Asn Leu Asp Ile Asp Asn  
 545 550 555 560

Met Arg His Lys Ile Arg Asp Tyr Ser Leu Ser Gly Ala Tyr Arg Lys  
 565 570 575

Ile Ile Ile Arg Pro Gln Asn Val Ser Trp Glu Val Val Ala Tyr Asp  
 580 585 590

Asp Pro Lys Ile Pro Leu Phe Asn Thr Asp Val Asp Asn Leu Glu Gly  
 595 600 605

Lys Thr Pro Pro Val Phe Ala Ser Glu Gly Lys Tyr Arg Ala Leu Lys  
 610 615 620

Met Asp Phe Ser Leu Pro Pro Ser Thr Tyr Ala Thr Met Ala Ile Arg  
 625 630 635 640

Glu Val Leu Lys Met Asp Thr Ser Ile Lys Asn Gln Thr Gln Leu Asn  
 645 650 655

Thr Thr Trp Leu Arg  
 660

<210> 182  
 <211> 396  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 182

Met Pro Pro Lys Lys Gly Gly Asp Gly Ile Lys Pro Pro Pro Ile Ile  
1 5 10 15

Gly Arg Phe Gly Thr Ser Leu Lys Ile Gly Ile Val Gly Leu Pro Asn  
20 25 30

Val Gly Lys Ser Thr Phe Phe Asn Val Leu Thr Asn Ser Gln Ala Ser  
35 40 45

Ala Glu Asn Phe Pro Phe Cys Thr Ile Asp Pro Asn Glu Ser Arg Val  
50 55 60

Pro Val Pro Asp Glu Arg Phe Asp Phe Leu Cys Gln Tyr His Lys Pro  
65 70 75 80

Ala Ser Lys Ile Pro Ala Phe Leu Asn Val Val Asp Ile Ala Gly Leu  
85 90 95

Val Lys Gly Ala His Asn Gly Gln Gly Leu Gly Asn Ala Phe Leu Ser  
100 105 110

His Ile Ser Ala Cys Asp Gly Ile Phe His Leu Thr Arg Ala Phe Glu  
115 120 125

Asp Asp Asp Ile Thr His Val Glu Gly Ser Val Asp Pro Ile Arg Asp  
130 135 140

Ile Glu Ile Ile His Glu Glu Leu Gln Leu Lys Asp Glu Glu Met Ile  
145 150 155 160

Gly Pro Ile Ile Asp Lys Leu Glu Lys Val Ala Val Arg Gly Gly Asp  
165 170 175

Lys Lys Leu Lys Pro Glu Tyr Asp Ile Met Cys Lys Val Lys Ser Trp  
180 185 190

Val Ile Asp Gln Lys Lys Pro Val Arg Phe Tyr His Asp Trp Asn Asp  
195 200 205

Lys Glu Ile Glu Val Leu Asn Lys His Leu Phe Leu Thr Ser Lys Pro  
210 215 220

Met Val Tyr Leu Val Asn Leu Ser Glu Lys Asp Tyr Ile Arg Lys Lys  
225 230 235 240

Asn Lys Trp Leu Ile Lys Ile Lys Glu Trp Val Asp Lys Tyr Asp Pro



245                      250                      255  
 Gly Ala Leu Val Ile Pro Phe Ser Gly Ala Leu Glu Leu Lys Leu Gln  
                          260                      265                      270  
 Glu Leu Ser Ala Glu Glu Arg Gln Lys Tyr Leu Glu Ala Asn Met Thr  
                          275                      280                      285  
 Gln Ser Ala Leu Pro Lys Ile Ile Lys Ala Gly Phe Ala Ala Leu Gln  
                          290                      295                      300  
 Leu Glu Tyr Phe Phe Thr Ala Gly Pro Asp Glu Val Arg Ala Trp Thr  
                          305                      310                      315                      320  
 Ile Arg Lys Gly Thr Lys Ala Pro Gln Ala Ala Gly Lys Ile His Thr  
                          325                      330                      335  
 Asp Phe Glu Lys Gly Phe Ile Met Ala Glu Val Met Lys Tyr Glu Asp  
                          340                      345                      350  
 Phe Lys Glu Glu Gly Ser Glu Asn Ala Val Lys Ala Ala Gly Lys Tyr  
                          355                      360                      365  
 Arg Gln Gln Gly Arg Asn Tyr Ile Val Glu Asp Gly Asp Ile Ile Phe  
                          370                      375                      380  
 Phe Lys Phe Asn Thr Pro Gln Gln Pro Lys Lys Lys  
                          385                      390                      395

<210> 183  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<400> 183

Pro Gly Leu Val Asp Ser Asn Pro Ala Pro Pro Glu Ser Gln Glu Lys  
 1                      5                      10                      15  
 Lys Pro Leu Lys Pro Cys Cys Ala Cys Pro Glu Thr Lys Lys Ala Arg  
                          20                      25                      30  
 Asp Ala Cys Ile Ile Glu Lys Gly Glu Glu His Cys Gly His Leu Ile  
                          35                      40                      45  
 Glu Ala His Lys Glu Cys Met Arg Ala Leu Gly Phe Lys Ile  
                          50                      55                      60

<210> 184  
 <211> 182

<212> PRT  
 <213> Homo sapiens

<400> 184

Met Pro Leu Ser Gln Ile Lys Lys Val Leu Asp Ile Arg Glu Thr Glu  
 1 5 10 15

Asp Cys His Asn Ala Phe Ala Leu Leu Val Arg Pro Pro Thr Glu Gln  
 20 25 30

Ala Asn Val Leu Leu Ser Phe Gln Met Thr Ser Asp Glu Leu Pro Lys  
 35 40 45

Glu Asn Trp Leu Lys Met Leu Cys Arg His Val Ala Asn Thr Ile Cys  
 50 55 60

Lys Ala Asp Ala Glu Asn Leu Ile Tyr Thr Ala Asp Pro Glu Ser Phe  
 65 70 75 80

Glu Val Asn Thr Lys Asp Met Asp Ser Thr Leu Ser Arg Ala Ser Arg  
 85 90 95

Ala Ile Lys Lys Thr Ser Lys Lys Val Thr Arg Ala Phe Ser Phe Ser  
 100 105 110

Lys Thr Pro Lys Arg Ala Leu Arg Arg Ala Leu Met Thr Ser His Gly  
 115 120 125

Ser Val Glu Gly Arg Ser Pro Ser Ser Asn Asp Lys His Val Met Ser  
 130 135 140

Arg Leu Ser Ser Thr Ser Ser Leu Ala Gly Ile Pro Ser Pro Ser Leu  
 145 150 155 160

Val Ser Leu Pro Ser Phe Phe Glu Arg Arg Ser His Thr Leu Ser Arg  
 165 170 175

Ser Thr Thr His Leu Ile  
 180

<210> 185  
 <211> 583  
 <212> PRT  
 <213> Homo sapiens

<400> 185

Pro Leu Lys Glu Gly Arg Val Arg Glu Ile Met Thr Phe Leu Val Asn  
 1 5 10 15

Asp Val Leu Lys His Gln Ala Ile Leu Leu Gly Asn Ala Glu Glu Gln  
 20 25 30  
 Lys Lys Lys Lys Arg Ser Leu Trp Asp Thr Ile Lys Lys Lys Lys Ile  
 35 40 45  
 Ser Ala Ser Thr Ser His Asn Arg Arg Val Ser Asn Ile Gln Asn Val  
 50 55 60  
 Asn Lys Thr Phe Ser Val Ser Gln Lys Val Asp Arg Val Arg Ser Pro  
 65 70 75 80  
 Leu Gln Ala Cys Glu Asn Leu Ala Met Asn Glu Gly Gly Pro Pro Thr  
 85 90 95  
 Glu Asn Asn Ser Leu Ile Leu Glu Glu Asn Lys Ile Pro Ile Ser Pro  
 100 105 110  
 Ile Ser Pro Ala Phe Asn Glu Cys His Gly Ala Thr Cys Leu Pro Leu  
 115 120 125  
 Ser Val Arg Arg Ser Thr Thr Tyr Ser Ser Leu His Ala Ser Glu Asn  
 130 135 140  
 Arg Glu Leu Leu Asn Val His Ser Ala Asn Val Ser Lys Val Ser Phe  
 145 150 155 160  
 Asn Glu Lys Ala Val Thr Glu Thr Ser Phe Asn Ser Val Asn Val Asn  
 165 170 175  
 Gly Gln Arg Gly Glu Asn Ser Lys Leu Ser Leu Thr Pro Asn Cys Ser  
 180 185 190  
 Ser Thr Leu Asn Ile Thr Gln Ser Gln Ile His Phe Leu Ser Pro Asp  
 195 200 205  
 Ser Phe Val Asn Asn Ser His Gly Ala Asn Asn Glu Leu Glu Leu Val  
 210 215 220  
 Thr Cys Leu Ser Ser Asp Met Phe Met Lys Asp Asn Ser Gln Pro Val  
 225 230 235 240  
 His Leu Glu Ser Thr Ile Ala His Glu Ile Tyr Gln Lys Ile Leu Ser  
 245 250 255  
 Pro Asp Ser Phe Ile Lys Asp Asn Tyr Gly Leu Asn Gln Asp Leu Glu  
 260 265 270

Ser Glu Ser Val Asn Pro Ile Leu Ser Pro Asn Gln Phe Leu Lys Asp  
 275 280 285  
 Asn Met Ala Tyr Met Cys Thr Ser Gln Gln Thr Cys Lys Val Pro Leu  
 290 295 300  
 Ser Asn Glu Asn Ser Gln Val Pro Gln Ser Pro Glu Asp Trp Arg Lys  
 305 310 315 320  
 Ser Glu Val Ser Pro Arg Ile Pro Glu Cys Gln Gly Ser Lys Ser Pro  
 325 330 335  
 Lys Ala Ile Phe Glu Glu Leu Val Glu Met Lys Ser Asn Tyr Tyr Ser  
 340 345 350  
 Phe Ile Lys Gln Asn Asn Pro Lys Phe Ser Ala Val Gln Asp Ile Ser  
 355 360 365  
 Ser His Ser His Asn Lys Gln Pro Lys Arg Arg Pro Ile Leu Ser Ala  
 370 375 380  
 Thr Val Thr Lys Arg Lys Ala Thr Cys Thr Arg Glu Asn Gln Thr Glu  
 385 390 395 400  
 Ile Asn Lys Pro Lys Ala Lys Arg Cys Leu Asn Ser Ala Val Gly Glu  
 405 410 415  
 His Glu Lys Val Ile Asn Asn Gln Lys Glu Lys Glu Asp Phe His Ser  
 420 425 430  
 Tyr Leu Pro Ile Ile Asp Pro Ile Leu Ser Lys Ser Lys Ser Tyr Lys  
 435 440 445  
 Asn Glu Val Thr Pro Ser Ser Thr Thr Ala Ser Val Ala Arg Lys Arg  
 450 455 460  
 Lys Ser Asp Gly Ser Met Glu Asp Ala Asn Val Arg Val Ala Ile Thr  
 465 470 475 480  
 Glu His Thr Glu Val Arg Glu Ile Lys Arg Ile His Phe Ser Pro Ser  
 485 490 495  
 Glu Pro Lys Thr Ser Ala Val Lys Lys Thr Lys Asn Val Thr Thr Pro  
 500 505 510  
 Ile Ser Lys Arg Ile Ser Asn Arg Glu Lys Leu Asn Leu Lys Lys Lys  
 515 520 525

Thr Asp Leu Ser Ile Phe Arg Thr Pro Ile Ser Lys Thr Asn Lys Arg  
 530 535 540

Thr Lys Pro Ile Ile Ala Val Ala Gln Ser Ser Leu Thr Phe Ile Lys  
 545 550 555 560

Pro Leu Lys Thr Asp Ile Pro Arg His Pro Met Pro Phe Ala Ala Lys  
 565 570 575

Asn Met Phe Tyr Asp Glu Arg  
 580

<210> 186  
 <211> 749  
 <212> PRT  
 <213> Homo sapiens

<400> 186

Met Ala Leu Pro Leu Leu Pro Gly Asn Ser Phe Asn Arg Asn Val Gly  
 1 5 10 15

Lys Glu Lys Phe His Lys Ser Gln His Trp Gly Phe Cys Asn Asn Val  
 20 25 30

Met Met Leu Val Ser Asp Glu Lys Pro Gly Ile Gly Gly Glu Pro Leu  
 35 40 45

Leu Gly Gln Lys Ile Lys Pro Lys Cys Ser Ile Tyr Pro Lys Gly Asp  
 50 55 60

Gly Ser Asp Val Pro Ser Trp Val Ala Phe Asp Lys Gln Val Leu Ser  
 65 70 75 80

Phe Asp Ala Tyr Leu Glu Glu Glu Val Leu Asp Lys Ser Gln Thr Asn  
 85 90 95

Tyr Arg Ile Arg Tyr Tyr Lys Ile Tyr Phe Tyr Pro Glu Asp Asp Thr  
 100 105 110

Ile Gln Val Asn Glu Pro Glu Val Lys Asn Ser Gly Leu Leu Gln Gly  
 115 120 125

Thr Ser Ile Arg Arg His Arg Ile Thr Leu Pro Pro Pro Asp Glu Asp  
 130 135 140

Gln Phe Tyr Thr Val Tyr His Phe Asn Val Gly Thr Glu Val Val Phe  
 145 150 155 160

Tyr Gly Arg Thr Phe Lys Ile Tyr Asp Cys Asp Ala Phe Thr Arg Asn

165 170 175  
 Phe Leu Arg Lys Ile Gly Val Lys Val Asn Pro Pro Val Gln Cys Pro  
 180 185 190  
 Glu Asp Pro Tyr Met Lys Ile Arg Arg Glu Val Val Glu His Val Glu  
 195 200 205  
 Pro Leu Arg Pro Tyr Glu Ser Leu Asp Thr Leu Lys Gln Phe Leu Gln  
 210 215 220  
 Tyr His Gly Lys Ile Leu Cys Phe Phe Cys Leu Trp Asp Asp Ser Val  
 225 230 235 240  
 Ser Met Phe Gly Asp Arg Arg Glu Leu Ile Leu His Tyr Phe Leu Cys  
 245 250 255  
 Asp Asp Thr Ile Glu Ile Lys Glu Leu Leu Pro His Ser Ser Gly Arg  
 260 265 270  
 Asp Ala Leu Lys Met Phe Leu Arg Arg Ser Lys Leu Pro Lys Asn Cys  
 275 280 285  
 Pro Pro Arg Val Tyr Gln Pro Gly Gln Ile Thr Asp Arg Ala Val Leu  
 290 295 300  
 Asn Ser Tyr Gly Asp Phe Ile Lys Asn Gln Ala Asp Gly Tyr Leu Phe  
 305 310 315 320  
 Asp Arg Tyr Lys Leu Gly Lys Val Asp Gln Glu Phe Tyr Lys Asp Ser  
 325 330 335  
 Asp Leu Ser Leu Gly Val Thr Ile Asn Val Trp Gly Arg Lys Val Leu  
 340 345 350  
 Leu Tyr Asp Cys Asp Glu Phe Thr Lys Ser Tyr Tyr Lys Ser Lys Tyr  
 355 360 365  
 Gly Ile Glu Asn Phe Thr Ser Val Ser Cys Lys Pro Pro Ser Pro Pro  
 370 375 380  
 Pro Lys Ile Glu Arg Lys Phe Pro Pro Tyr Asn Gly Phe Gly Ser Glu  
 385 390 395 400  
 Glu Asp Ser Leu Arg Asn Cys Ile Asp Leu Lys Pro Thr Pro His Arg  
 405 410 415  
 Arg Asn Phe Lys Lys Phe Met Glu Lys Asp Ser Tyr Gly Ser Lys Ser  
 420 425

503/514

675                      680                      685

Ile Asp Tyr Lys Ser Phe Phe Ser Ala Leu Asn Trp Arg Lys Asn Pro  
           690                      695                      700

Val Pro Glu Leu Gln Pro Ala Ser Tyr Leu Lys Glu Arg Cys Glu Asp  
           705                      710                      715                      720

Val Trp Leu Gly Met Pro Ser Pro Ile Pro Ala Lys Tyr Ile Asp Tyr  
                               725                      730                      735

Trp Thr Phe Leu Lys Asp Ala Phe Gly Leu Glu Glu Glu  
                               740                      745

<210> 187  
 <211> 588  
 <212> PRT  
 <213> Homo sapiens

<400> 187

Met Pro Gln Leu Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser Gly  
 1                      5                      10                      15

Gly Gly Gly Gly Ser Ser Ala Gly Ala Ala Gly Gly Gly Asp Asp Leu  
                               20                      25                      30

Gly Ala Asn Asp Glu Leu Ile Pro Phe Gln Asp Glu Gly Gly Glu Glu  
                               35                      40                      45

Gln Glu Pro Ser Ser Asp Ser Ala Ser Ala Gln Arg Asp Leu Asp Glu  
                               50                      55                      60

Val Lys Ser Ser Leu Val Asn Glu Ser Glu Asn Gln Ser Ser Ser Ser  
                               65                      70                      75                      80

Asp Ser Glu Ala Glu Arg Arg Pro Gln Pro Val Arg Asp Thr Phe Gln  
                               85                      90                      95

Lys Pro Arg Asp Tyr Phe Ala Glu Val Arg Arg Pro Gln Asp Ser Ala  
                               100                      105                      110

Phe Phe Lys Gly Pro Pro Tyr Pro Gly Tyr Pro Phe Leu Met Ile Pro  
                               115                      120                      125

Asp Leu Ser Ser Pro Tyr Leu Ser Asn Gly Pro Leu Ser Pro Gly Gly  
                               130                      135                      140

Ala Arg Thr Tyr Leu Gln Met Lys Trp Pro Leu Leu Asp Val Pro Ser  
                               145                      150                      155                      160



Ser Ala Thr Val Lys Asp Thr Arg Ser Pro Ser Pro Ala His Leu Ser  
 165 170 175  
 Asn Lys Val Pro Val Val Gln His Pro His His Met His Pro Leu Thr  
 180 185 190  
 Pro Leu Ile Thr Tyr Ser Asn Asp His Phe Ser Pro Gly Ser Pro Pro  
 195 200 205  
 Thr His Leu Ser Pro Glu Ile Asp Pro Lys Thr Gly Ile Pro Arg Pro  
 210 215 220  
 Pro His Pro Ser Glu Leu Ser Pro Tyr Tyr Pro Leu Ser Pro Gly Ala  
 225 230 235 240  
 Val Gly Gln Ile Pro His Pro Leu Gly Trp Leu Val Pro Gln Gln Gly  
 245 250 255  
 Gln Pro Met Tyr Ser Leu Pro Pro Gly Gly Phe Arg His Pro Tyr Pro  
 260 265 270  
 Ala Leu Ala Met Asn Ala Ser Met Ser Ser Leu Val Ser Ser Arg Phe  
 275 280 285  
 Ser Pro His Met Val Ala Pro Ala His Pro Gly Leu Pro Thr Ser Gly  
 290 295 300  
 Ile Pro His Pro Ala Ile Val Ser Pro Ile Val Lys Gln Glu Pro Ala  
 305 310 315 320  
 Pro Pro Ser Leu Ser Pro Ala Val Ser Val Lys Ser Pro Val Thr Val  
 325 330 335  
 Lys Lys Glu Glu Glu Lys Lys Pro His Val Lys Lys Pro Leu Asn Ala  
 340 345 350  
 Phe Met Leu Tyr Met Lys Glu Met Arg Ala Lys Val Val Ala Glu Cys  
 355 360 365  
 Thr Leu Lys Glu Ser Ala Ala Ile Asn Gln Ile Leu Gly Arg Lys Trp  
 370 375 380  
 His Asn Leu Ser Arg Glu Glu Gln Ala Lys Tyr Tyr Glu Leu Ala Arg  
 385 390 395 400  
 Lys Glu Arg Gln Leu His Ser Gln Leu Tyr Pro Thr Trp Ser Ala Arg  
 405 410 415

Asp Asn Tyr Gly Lys Lys Lys Lys Arg Lys Arg Glu Lys Gln Leu Ser  
 420 425 430

Gln Thr Gln Ser Gln Gln Gln Val Gln Glu Ala Glu Gly Ala Leu Ala  
 435 440 445

Ser Lys Ser Lys Lys Pro Cys Val Gln Tyr Leu Pro Pro Glu Lys Pro  
 450 455 460

Cys Asp Ser Pro Ala Ser Ser His Gly Ser Met Leu Asp Ser Pro Ala  
 465 470 475 480

Thr Pro Ser Ala Ala Leu Ala Ser Pro Ala Ala Pro Ala Ala Thr His  
 485 490 495

Ser Glu Gln Ala Gln Pro Leu Ser Leu Thr Thr Lys Pro Glu Thr Arg  
 500 505 510

Ala Gln Leu Ala Leu His Ser Ala Ala Phe Leu Ser Ala Lys Ala Ala  
 515 520 525

Ala Ser Ser Ser Gly Gln Met Gly Ser Gln Pro Pro Leu Leu Ser Arg  
 530 535 540

Pro Leu Pro Leu Gly Ser Met Pro Thr Ala Leu Leu Ala Ser Pro Pro  
 545 550 555 560

Ser Phe Pro Ala Thr Leu His Ala His Gln Ala Leu Pro Val Leu Gln  
 565 570 575

Ala Gln Pro Leu Ser Leu Val Thr Lys Ser Ala His  
 580 585

<210> 188  
 <211> 196  
 <212> PRT  
 <213> Homo sapiens

<400> 188

Met Ala Asp Gly Gln Met Pro Phe Ser Cys His Tyr Pro Ser Arg Leu  
 1 5 10 15

Arg Arg Asp Pro Phe Arg Asp Ser Pro Leu Ser Ser Arg Leu Leu Asp  
 20 25 30

Asp Gly Phe Gly Met Asp Pro Phe Pro Asp Asp Leu Thr Ala Ser Trp  
 35 40 45

Pro Asp Trp Ala Leu Pro Arg Leu Ser Ser Ala Trp Pro Gly Thr Leu  
 50 55 60

Arg Ser Gly Met Val Pro Arg Gly Pro Thr Ala Thr Ala Arg Phe Gly  
 65 70 75 80

Val Pro Ala Glu Gly Arg Thr Pro Pro Phe Pro Gly Glu Pro Trp  
 85 90 95

Lys Val Cys Val Asn Val His Ser Phe Lys Pro Glu Glu Leu Met Val  
 100 105 110

Lys Thr Lys Asp Gly Tyr Val Glu Val Ser Gly Lys His Glu Glu Lys  
 115 120 125

Gln Gln Glu Gly Gly Ile Val Ser Lys Asn Phe Thr Lys Lys Ile Gln  
 130 135 140

Leu Pro Ala Glu Val Asp Pro Val Thr Val Phe Ala Ser Leu Ser Pro  
 145 150 155 160

Glu Gly Leu Leu Ile Ile Glu Ala Pro Gln Val Pro Pro Tyr Ser Thr  
 165 170 175

Phe Gly Glu Ser Ser Phe Asn Asn Glu Leu Pro Gln Asp Ser Gln Glu  
 180 185 190

Val Thr Cys Thr  
 195

<210> 189  
 <211> 890  
 <212> PRT  
 <213> Homo sapiens

<400> 189

Met Glu Tyr Glu Trp Lys Pro Asp Glu Gln Gly Leu Gln Gln Ile Leu  
 1 5 10 15

Gln Leu Leu Lys Glu Ser Gln Ser Pro Asp Thr Thr Ile Gln Arg Thr  
 20 25 30

Val Gln Gln Lys Leu Glu Gln Leu Asn Gln Tyr Pro Asp Phe Asn Asn  
 35 40 45

Tyr Leu Ile Phe Val Leu Thr Lys Leu Lys Ser Glu Asp Glu Pro Thr  
 50 55 60

- 507

Arg Ser Leu Ser Gly Leu Ile Leu Lys Asn Asn Val Lys Ala His Phe  
65 70 75 80

Gln Asn Phe Pro Asn Gly Val Thr Asp Phe Ile Lys Ser Glu Cys Leu  
85 90 95

Asn Asn Ile Gly Asp Ser Ser Pro Leu Ile Arg Ala Thr Val Gly Ile  
100 105 110

Leu Ile Thr Thr Ile Ala Ser Lys Gly Glu Leu Gln Asn Trp Pro Asp  
115 120 125

Leu Leu Pro Lys Leu Cys Ser Leu Leu Asp Ser Glu Asp Tyr Asn Thr  
130 135 140

Cys Glu Gly Ala Phe Gly Ala Leu Gln Lys Ile Cys Glu Asp Ser Ala  
145 150 155 160

Glu Ile Leu Asp Ser Asp Val Leu Asp Arg Pro Leu Asn Ile Met Ile  
165 170 175

Pro Lys Phe Leu Gln Phe Phe Lys His Ser Ser Pro Lys Ile Arg Ser  
180 185 190

His Ala Val Ala Cys Val Asn Gln Phe Ile Ile Ser Arg Thr Gln Ala  
195 200 205

Leu Met Leu His Ile Asp Ser Phe Ile Glu Asn Leu Phe Ala Leu Ala  
210 215 220

Gly Asp Glu Glu Pro Glu Val Arg Lys Asn Val Cys Arg Ala Leu Val  
225 230 235 240

Met Leu Leu Glu Val Arg Met Asp Arg Leu Leu Pro His Met His Asn  
245 250 255

Ile Val Glu Tyr Met Leu Gln Arg Thr Gln Asp Gln Asp Glu Asn Val  
260 265 270

Ala Leu Glu Ala Cys Glu Phe Trp Leu Thr Leu Ala Glu Gln Pro Ile  
275 280 285

Cys Lys Asp Val Leu Val Arg His Leu Pro Lys Leu Ile Pro Val Leu  
290 295 300

Val Asn Gly Met Lys Tyr Ser Asp Ile Asp Ile Ile Leu Leu Lys Gly  
305 310 315 320

Asp Val Glu Glu Asp Glu Thr Ile Pro Asp Ser Glu Gln Asp Ile Arg  
 325 330 335  
 Pro Arg Phe His Arg Ser Arg Thr Val Ala Gln Gln His Asp Glu Asp  
 340 345 350  
 Gly Ile Glu Glu Glu Asp Asp Asp Asp Asp Glu Ile Asp Asp Asp Asp  
 355 360 365  
 Thr Ile Ser Asp Trp Asn Leu Arg Lys Cys Ser Ala Ala Ala Leu Asp  
 370 375 380  
 Val Leu Ala Asn Val Tyr Arg Asp Glu Leu Leu Pro His Ile Leu Pro  
 385 390 395 400  
 Leu Leu Lys Glu Leu Leu Phe His His Glu Trp Val Val Lys Glu Ser  
 405 410 415  
 Gly Ile Leu Val Leu Gly Ala Ile Ala Glu Gly Cys Met Gln Gly Met  
 420 425 430  
 Ile Pro Tyr Leu Pro Glu Leu Ile Pro His Leu Ile Gln Cys Leu Ser  
 435 440 445  
 Asp Lys Lys Ala Leu Val Arg Ser Ile Thr Cys Trp Thr Leu Ser Arg  
 450 455 460  
 Tyr Ala His Trp Val Val Ser Gln Pro Pro Asp Thr Tyr Leu Lys Pro  
 465 470 475 480  
 Leu Met Thr Glu Leu Leu Lys Arg Ile Leu Asp Ser Asn Lys Arg Val  
 485 490 495  
 Gln Glu Ala Ala Cys Ser Ala Phe Ala Thr Leu Glu Glu Glu Ala Cys  
 500 505 510  
 Thr Glu Leu Val Pro Tyr Leu Ala Tyr Ile Leu Asp Thr Leu Val Phe  
 515 520 525  
 Ala Phe Ser Lys Tyr Gln His Lys Asn Leu Leu Ile Leu Tyr Asp Ala  
 530 535 540  
 Ile Gly Thr Leu Ala Asp Ser Val Gly His His Leu Asn Lys Pro Glu  
 545 550 555 560  
 Tyr Ile Gln Met Leu Met Pro Pro Leu Ile Gln Lys Trp Asn Met Leu  
 565 570 575

Lys Asp Glu Asp Lys Asp Leu Phe Pro Leu Leu Glu Cys Leu Ser Ser  
 580 585 590  
 Val Ala Thr Ala Leu Gln Ser Gly Phe Leu Pro Tyr Cys Glu Pro Val  
 595 600 605  
 Tyr Gln Arg Cys Val Asn Leu Val Gln Lys Thr Leu Ala Gln Ala Met  
 610 615 620  
 Leu Asn Asn Ala Gln Pro Asp Gln Tyr Glu Ala Pro Asp Lys Asp Phe  
 625 630 635 640  
 Met Ile Val Ala Leu Asp Leu Leu Ser Gly Leu Ala Glu Gly Leu Gly  
 645 650 655  
 Gly Asn Ile Glu Gln Leu Val Ala Arg Ser Asn Ile Leu Thr Leu Met  
 660 665 670  
 Tyr Gln Cys Met Gln Asp Lys Met Pro Glu Val Arg Gln Ser Ser Phe  
 675 680 685  
 Ala Leu Leu Gly Asp Leu Thr Lys Ala Cys Phe Gln His Val Lys Pro  
 690 695 700  
 Cys Ile Ala Asp Phe Met Pro Ile Leu Gly Thr Asn Leu Asn Pro Glu  
 705 710 715 720  
 Phe Ile Ser Val Cys Asn Asn Ala Thr Trp Ala Ile Gly Glu Ile Ser  
 725 730 735  
 Ile Gln Met Gly Ile Glu Met Gln Pro Tyr Ile Pro Met Val Leu His  
 740 745 750  
 Gln Leu Val Glu Ile Ile Asn Arg Pro Asn Thr Pro Lys Thr Leu Leu  
 755 760 765  
 Glu Asn Thr Ala Ile Thr Ile Gly Arg Leu Gly Tyr Val Cys Pro Gln  
 770 775 780  
 Glu Val Ala Pro Met Leu Gln Gln Phe Ile Arg Pro Trp Cys Thr Ser  
 785 790 795 800  
 Leu Arg Asn Ile Arg Asp Asn Glu Glu Lys Asp Ser Ala Phe Arg Gly  
 805 810 815  
 Ile Cys Thr Met Ile Ser Val Asn Pro Ser Gly Val Ile Gln Asp Phe  
 820 825 830

Ile Phe Phe Cys Asp Ala Val Ala Ser Trp Ile Asn Pro Lys Asp Asp  
835 840 845

Leu Arg Asp Met Phe Cys Lys Ile Leu His Gly Phe Lys Asn Gln Val  
850 855 860

Gly Asp Glu Asn Trp Arg Arg Phe Ser Asp Gln Phe Pro Leu Pro Leu  
865 870 875 880

Lys Glu Arg Leu Ala Ala Phe Tyr Gly Val  
885 890

<210> 190  
<211> 449  
<212> PRT  
<213> Homo sapiens

<400> 190

Met Met Lys Thr Leu Leu Leu Phe Val Gly Leu Leu Leu Thr Trp Glu  
1 5 10 15

Ser Gly Gln Val Leu Gly Asp Gln Thr Val Ser Asp Asn Glu Leu Gln  
20 25 30

Glu Met Ser Asn Gln Gly Ser Lys Tyr Val Asn Lys Glu Ile Gln Asn  
35 40 45

Ala Val Asn Gly Val Lys Gln Ile Lys Thr Leu Ile Glu Lys Thr Asn  
50 55 60

Glu Glu Arg Lys Thr Leu Leu Ser Asn Leu Glu Glu Ala Lys Lys Lys  
65 70 75 80

Lys Glu Asp Ala Leu Asn Glu Thr Arg Glu Ser Glu Thr Lys Leu Lys  
85 90 95

Glu Leu Pro Gly Val Cys Asn Glu Thr Met Met Ala Leu Trp Glu Glu  
100 105 110

Cys Lys Pro Cys Leu Lys Gln Thr Cys Met Lys Phe Tyr Ala Arg Val  
115 120 125

Cys Arg Ser Gly Ser Gly Leu Val Gly Arg Gln Leu Glu Glu Phe Leu  
130 135 140

Asn Gln Ser Ser Pro Phe Tyr Phe Trp Met Asn Gly Asp Arg Ile Asp  
145 150 155 160

Ser Leu Leu Glu Asn Asp Arg Gln Gln Thr His Met Leu Asp Val Met

165 170 175  
 Gln Asp His Phe Ser Arg Ala Ser Ser Ile Ile Asp Glu Leu Phe Gln  
 180 185 190  
 Asp Arg Phe Phe Thr Arg Glu Pro Gln Asp Thr Tyr His Tyr Leu Pro  
 195 200 205  
 Phe Ser Leu Pro His Arg Arg Pro His Phe Phe Phe Pro Lys Ser Arg  
 210 215 220  
 Ile Val Arg Ser Leu Met Pro Phe Ser Pro Tyr Glu Pro Leu Asn Phe  
 225 230 235 240  
 His Ala Met Phe Gln Pro Phe Leu Glu Met Ile His Glu Ala Gln Gln  
 245 250 255  
 Ala Met Asp Ile His Phe His Ser Pro Ala Phe Gln His Pro Pro Thr  
 260 265 270  
 Glu Phe Ile Arg Glu Gly Asp Asp Asp Arg Thr Val Cys Arg Glu Ile  
 275 280 285  
 Arg His Asn Ser Thr Gly Cys Leu Arg Met Lys Asp Gln Cys Asp Lys  
 290 295 300  
 Cys Arg Glu Ile Leu Ser Val Asp Cys Ser Thr Asn Asn Pro Ser Gln  
 305 310 315 320  
 Ala Lys Leu Arg Arg Glu Leu Asp Glu Ser Leu Gln Val Ala Glu Arg  
 325 330 335  
 Leu Thr Arg Lys Tyr Asn Glu Leu Leu Lys Ser Tyr Gln Trp Lys Met  
 340 345 350  
 Leu Asn Thr Ser Ser Leu Leu Glu Gln Leu Asn Glu Gln Phe Asn Trp  
 355 360 365  
 Val Ser Arg Leu Ala Asn Leu Thr Gln Gly Glu Asp Gln Tyr Tyr Leu  
 370 375 380  
 Arg Val Thr Thr Val Ala Ser His Thr Ser Asp Ser Asp Val Pro Ser  
 385 390 395 400  
 Gly Val Thr Glu Val Val Val Lys Leu Phe Asp Ser Asp Pro Ile Thr  
 405 410 415  
 Val Thr Val Pro Val Glu Val Ser Arg Lys Asn Pro Lys Phe Met Glu



420

425

430

Thr Val Ala Glu Lys Ala Leu Gln Glu Tyr Arg Lys Lys His Arg Glu  
 435 440 445

Glu

<210> 191  
 <211> 361  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 191

Met Tyr Gly Arg Asn Glu Leu Ile Ala Arg Tyr Ile Lys Leu Arg Thr  
 1 5 10 15

Gly Lys Thr Arg Thr Arg Lys Gln Val Ser Ser His Ile Gln Val Leu  
 20 25 30

Ala Arg Arg Lys Ala Arg Glu Ile Gln Ala Lys Leu Lys Asp Gln Ala  
 35 40 45

Ala Lys Asp Lys Ala Leu Gln Ser Met Ala Ala Met Ser Ser Ala Gln  
 50 55 60

Ile Ile Ser Ala Thr Ala Phe His Ser Ser Met Ala Leu Ala Arg Gly  
 65 70 75 80

Pro Gly Arg Pro Ala Val Ser Gly Phe Trp Gln Gly Ala Leu Pro Gly  
 85 90 95

Gln Ala Gly Thr Ser His Asp Val Lys Pro Phe Ser Gln Gln Thr Tyr  
 100 105 110

Ala Val Gln Pro Pro Leu Pro Leu Pro Gly Phe Glu Ser Pro Ala Gly  
 115 120 125

Pro Ala Pro Ser Pro Ser Ala Pro Pro Ala Pro Pro Trp Gln Gly Arg  
 130 135 140

Ser Val Ala Ser Ser Lys Leu Trp Met Leu Glu Phe Ser Ala Phe Leu  
 145 150 155 160

Glu Gln Gln Gln Asp Pro Asp Thr Tyr Asn Lys His Leu Phe Val His  
 165 170 175

Ile Gly Gln Ser Ser Pro Ser Tyr Ser Asp Pro Tyr Leu Glu Ala Val  
 180 185 190

Asp Ile Arg Gln Ile Tyr Asp Lys Phe Pro Glu Lys Lys Gly Gly Leu  
 195 200 205

Lys Asp Leu Phe Glu Arg Gly Pro Ser Asn Ala Phe Phe Leu Val Lys  
 210 215 220

Phe Trp Ala Asp Leu Asn Thr Asn Ile Glu Asp Glu Gly Ser Ser Phe  
 225 230 235 240

Tyr Gly Val Ser Ser Gln Tyr Glu Ser Pro Glu Asn Met Ile Ile Thr  
 245 250 255

Cys Ser Thr Lys Val Cys Ser Phe Gly Lys Gln Val Val Glu Lys Val  
 260 265 270

Glu Thr Glu Tyr Ala Arg Tyr Glu Asn Gly His Tyr Ser Tyr Arg Ile  
 275 280 285

His Arg Ser Pro Leu Cys Glu Tyr Met Ile Asn Phe Ile His Lys Leu  
 290 295 300

Lys His Leu Pro Glu Lys Tyr Met Met Asn Ser Val Leu Glu Asn Phe  
 305 310 315 320

Thr Ile Leu Gln Val Val Thr Asn Arg Asp Thr Gln Glu Thr Leu Leu  
 325 330 335

Cys Ile Ala Tyr Val Phe Glu Val Ser Ala Ser Glu His Gly Ala Gln  
 340 345 350

His His Ile Tyr Arg Leu Val Lys Glu  
 355 360